FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Afternoon Session

Thursday, April 30, 2026

1:00 p.m. to 4:53 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Joyce Frimpong, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Toni K. Choueiri, MD

Director, Lank Center for Genitourinary Oncology

Professor, Harvard Medical School

Dana-Farber Cancer Institute

Boston, Massachusetts

William J. Gradishar, MD

(via video conferencing platform)

Betsy Bramsen Professor of Breast Oncology and Professor of Medicine
Deputy Director, Clinical Network
Director, Maggie Daley Center for Women's Cancer Care
Robert H. Lurie Comprehensive Cancer Center
Feinberg School of Medicine at Northwestern University
Chicago, Illinois

Neil Vasan, MD, PhD

(Acting Chairperson)

Assistant Professor
Director, Breast Cancer Translational Research
Department of Medicine, NYU Grossman School of Medicine
Perlmutter Cancer Center, NYU Langone Health
New York, New York

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS

(Non-Voting)

Tara L. Frenkl, MD, MPH

Senior Vice President, Head of Global Medical Strategy and Evidence Generation

Bayer Pharmaceuticals

Whippany, New Jersey

TEMPORARY MEMBERS (Voting)

Karla V. Ballman, PhD, FASCO

Professor, Biostatistics

Division Chair, Division of Clinical Trials & Biostatistics

Mayo Clinic

Rochester, Minnesota

Paul T. Conway

(Patient Representative Afternoon Session Only; via video conferencing platform)

Falls Church, Virginia

Franklin Huang, MD, PhD

(Afternoon Session Only)

Associate Professor

Departments of Medicine and Urology

University of California San Francisco

Staff Physician, San Francisco Veterans Affairs

Medical Center (VAMC)

Scientific Director, Sierra Pacific Precision

Oncology Clinical Research Center

San Francisco, California

Brian Rini, MD

(Afternoon Session Only, via video conferencing platform)

Professor of Medicine

Vanderbilt Ingram Cancer Center

Department of Hematology/Oncology

Vanderbilt University Medical Center

Nashville, Tennessee

Kyle Robinson, MD

(Afternoon Session Only)

Staff Physician

Corporal Michael J. Crescenz VA Medical Center

Associate Professor of Clinical Medicine

Division of Hematology-Oncology

University of Pennsylvania Perelman School of Medicine

Philadelphia, Pennsylvania

Aihua Edward Yen, MD

(Afternoon Session Only)

Assistant Professor

Department of Medicine, Section of Hematology/Oncology

Baylor College of Medicine

Genitourinary Medical Oncologist

Dan L Duncan Cancer Center

Houston VA Medical Center

Houston, Texas

FDA PARTICIPANTS (Non-Voting)

R. Angelo de Claro, MD

Director (Acting)

Oncology Center for Excellence, FDA

Director (Acting), Office of Oncologic Diseases (OOD), CDER, FDA

Laleh Amiri-Kordestani, MD

Director

Division of Oncology 1 (DO1)

OOD, Office of New Drugs (OND), CDER, FDA

Daniel Suzman, MD

(Afternoon Session Only)

Deputy Director

DO1, OOD, OND, CDER, FDA

Elaine Chang, MD

(Afternoon Session Only)

Clinical Team Leader

DO1, OOD, OND, CDER, FDA

Daniel Lee, MD, PhD

(Afternoon Session Only)

Clinical Reviewer

DO1, OOD, OND, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(1:00 p.m.)

Call to Order

Introduction of Committee

DR. VASAN: Good afternoon, and welcome. I would first like to remind everyone to please mute your line when you're not speaking. All members of the public are reminded to silence their phones and other devices, and to otherwise refrain from disrupting the meeting. Loud talking or applause may make it difficult for meeting participants and observers to hear the proceedings.

My name is Dr. Neil Vasan, and I will be chairing this meeting. I now call the afternoon session of the April 30, 2026 meeting of the Oncologic Drugs Advisory Committee to order. We'll start by going around the table and introducing ourselves by stating our names and affiliations. We'll start with the FDA to my left and go around the table.

DR. DE CLARO: Angelo de Claro, Acting Director, FDA Oncology Center of Excellence.

DR. AMIRI-KORDESTANI: Laleh Amiri-Kordestani, Division Director of Division of Oncology 1.

DR. SUZMAN: Daniel Suzman, Deputy Division Director, Division Oncology 1.

DR. CHANG: Elaine Chang, Clinical Team Leader, Division of Oncology 1.

DR. LEE: Daniel Lee, Clinical Reviewer, DO1.

DR. RINI: Brian Rini, GU Oncologist, Vanderbilt in Nashville.

MR. CONWAY: Paul Conway, Vice President of the American Association of Kidney Patients and Chair of Policy, prostate cancer survivor, 29-year kidney transplant recipient. Thank you.

DR. GRADISHAR: Bill Gradishar, Northwestern University.

DR. CHOUEIRI: Toni Choueiri, Dana-Farber Cancer Institute.

DR. VASAN: Neil Vasan, NYU Langone.

DR. FRIMPONG: Joyce Frimpong, Designated Federal Officer, FDA.

DR. HUANG: Franklin Huang, Prostate Cancer

Oncologist at UCSF in the San Francisco VA Medical Center.

DR. ROBINSON: Kyle Robinson, Medical Oncologist, University of Pennsylvania and the Philadelphia VA.

DR. YEN: Edward Yen, Medical Oncologist, Baylor College of Medicine and Houston, VA.

DR. BALLMAN: Karla Ballman, Biostatistician, Mayo Clinic.

DR. FRENKL: Tara Frenkl, Head of Global Medical and Evidence at Bayer Pharmaceuticals. I am the pharmaceutical industry representative.

DR. VASAN: For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this 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 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.

Dr. Frimpong will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. FRIMPONG: The FDA is convening today's meeting of the Oncologic Drugs Advisory Committee under the Federal Advisory Committee Act of 1972. At today's meeting, the committee will discuss supplemental new drug application 218197/S-004, for Truqap, capivasertib, tablets, submitted by

AstraZeneca Pharmaceuticals LP. The proposed indication is in combination with abiraterone for the treatment of adult patients with metastatic hormone-sensitive prostate cancer that is PTEN-deficient as detected by an FDA-approved test.

With the exception of the industry representative, the members of the committee are special or regular government employees and are subject to federal conflict of interest laws and regulations. Accordingly, FDA has reviewed the financial interests of the committee members for compliance with federal ethics and conflict of interest laws. We have screened the members for potential financial conflicts of interest related to today's meeting agenda, both their own interests and those that are imputed to them, including those of their spouses, minor children, and employers.

Based on the agenda for today's meeting and all financial interests reported by committee members, the FDA has determined that all members of this advisory committee are in compliance with federal ethics and conflict of interest laws, and

as a result, no conflict of interest waivers under 18 U.S.C. 208 have been issued in connection with this meeting.

Dr. Tara Frenkl of Bayer Pharmaceuticals is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Consistent with Commissioner Makary's April 17, 2025 statement, FDA is only including industry representatives in advisory committee meetings where required by statute. FDA is required to include an industry representative in today's meeting under 21 U.S.C. 355(n)(3)(c).

Industry representatives are not appointed as special government employees nor are they regular government employees. Industry representatives serve as non-voting members of the committee. Non-voting industry representatives represent all regulated industry and not any particular association, company, product, or ingredient, and bringing general industry perspective to the committee.

Under FDA regulations, although a non-voting

member serves in a representative capacity, the non-voting member shall exercise restraint in performing such functions and may not engage in unseemly advocacy or attempt to exert undue influence over the other members of the committee. FDA asks that all other participants, including the open public hearing speakers, advise the committee of any financial relationships that they have with any of affected firms, its products, and if known, its direct competitors.

We would like to remind the members that if the discussions involve any products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to inform the DFO and exclude themselves from the discussion, and their exclusion will be noted for the record. Thank you.

DR. VASAN: And for the record, due to unforeseen circumstances, Dr. Fatima Karzai will not be joining us today.

We will now proceed with FDA opening remarks by Dr. Elaine Chang.

FDA Opening Remarks - Elaine Chang

DR. CHANG: Good afternoon. My name is Elaine Chang. I'm a Medical Oncologist and Team Leader in the Division of Oncology 1. I'd like to extend my thanks to the members of the advisory committee, the AstraZeneca team, invited guests, visitors, and FDA colleagues for attending and participating in today's discussion of the supplemental application for capivasertib, NDA 218197. In my introductory comments, I will provide a brief background on the application, FDA's reasons for requesting input from the committee, and the issues that FDA has identified for consideration during today's discussion.

Capivasertib is an AKT kinase inhibitor. The FDA approved it in 2023 for advanced breast cancer with PIK3CA, AKT1, or PTEN alterations. AstraZeneca, who I will refer to as the applicant, seeks approval of capivasertib in combination with abiraterone for the treatment of metastatic hormone-sensitive prostate cancer, mHSPC, with PTEN deficiency.

Results of the CAPItello-281 trial provide

the primary evidence to support the safety and efficacy of capivasertib in combination with abiraterone for the proposed indication. As depicted in this slide, CAPItello-281 is a double-blind, randomized, placebo-controlled, multicenter trial. It randomized 1,012 patients with mHSPC and PTEN loss to receive either capivasertib or placebo, in combination with abiraterone and prednisone or prednisolone, until disease progression or intolerable toxicity. Patients were required to have a hemoglobin A1C of less than 8 percent, and patients with diabetes could not be on insulin, given concerns around hyperglycemia, based on prior experience with capivasertib.

The primary efficacy outcome measure was radiographic progression-free survival, rPFS, according to investigator assessment using Response Evaluation Criteria for Solid Tumors Version 1.1 and Prostate Cancer Working Group 3 criteria. This means that progression events can be called based on either CT or bone scans, which is an acceptable definition of rPFS.

When the study design was proposed in 2020, the FDA stated that while rPFS is an acceptable primary endpoint, the clinical benefit of any improvement in rPFS would be assessed in terms of the magnitude of improvement and the consistency across other endpoints, particularly endpoints that measure how a patient feels, functions, or survives. The FDA stated that an improvement in overall survival or other clinically meaningful endpoints may be needed to demonstrate clinical benefit in the absence of a large magnitude of improvement in rPFS.

The primary analysis of CAPItello-281 demonstrated a statistically significant improvement in rPFS as assessed by investigator in patients randomized to receive capivasertib compared to patients randomized to placebo. The hazard ratio for rPFS was 0.81, with a 95 percent confidence interval that excludes 1. The estimated median rPFS was 33 months in the capivasertib arm and 26 months in the placebo arm. However, median rPFS estimates based on the rPFS Kaplan-Meier curves alone do not adequately characterize the treatment effect of rPFS

over time. We note that the median difference occurs at a point in the Kaplan-Meier curves where the difference between arms appears larger than at other points. Overall, the Kaplan-Meier curves and hazard ratio provide a more comprehensive summary of rPFS results than the median alone, and these both suggest a modest treatment effect.

Overall survival results were not statistically significant at interim analysis and are immature, with about 50 percent of the deaths expected at the final analysis. According to the applicant, the study was not powered to detect an overall survival benefit. Interim analysis results did not appear to show a detriment in OS. However, in the absence of a large improvement in rPFS, and considering the added toxicity of capivasertib, which we will discuss soon, a statistically significant improvement in OS may be needed to support a clinically meaningful treatment effect. Taken in totality, we are concerned that the rPFS result without an OS benefit may not represent clinically meaningful treatment effect.

The CAPItello-281 results are not consistent with prior trial results that have led to approvals for other drugs for patients with mHSPC. All prior approvals were either supported by a clinically meaningful treatment effect in rPFS with large magnitude of effect, OS benefit, or both. The trials that included rPFS as a primary endpoint were TITAN, ARCHES, ARANOTE, and AMPLITUDE.

While the approvals of apalutamide , enzalutamide, and darolutamide, all in combination with ADT, were supported by trials that randomized patients to doublet therapy versus placebo with ADT, the most contemporary trial was AMPLITUDE, which randomized patients to niraparib with abiraterone versus the same control arm as CAPItello-281, placebo and abiraterone. This trial demonstrated a clinically meaningful rPFS hazard ratio of 0.46 in the indicated population of patients with BRCA2-mutated mHSPC, supported by numerically favorable while immature overall survival results.

The other approvals that FDA has granted for mHSPC were supported by LATITUDE and ARASENS. Both

had OS as a primary endpoint and showed statistically significant OS effects with hazard ratio point estimates of 0.62 and 0.68, respectively. The approval of darolutamide with docetaxel and ADT was a contemporary trial with an active control arm therapy of docetaxel with ADT.

In totality, past FDA approvals for therapies and mHSPC have been supported by clinically meaningful treatment effects on rPFS, or OS, or both. This historical context informs the assessment of the clinical meaningfulness of the treatment effect observed in CAPItello-281. While not establishing a threshold treatment effect for approval, the FDA evaluates each application individually, based on the totality of evidence, including the magnitude of effect, toxicity, and meaningfulness in the clinical context.

In CAPItello-281, patients receiving capivasertib experienced a higher incidence of grade 3 or higher adverse reactions, serious adverse reactions, and adverse reactions leading to death. Toxicities occurring at a higher incidence in the

investigational arm included skin reactions, diarrhea, infections, and hyperglycemia, leading to high rates of drug discontinuation. Additionally, 44 percent of patients who received capivasertib required initiation or change in antihyperglycemic regimen, including 17 percent of all patients receiving capivasertib requiring initiation of insulin.

The proposed regimen includes a steroid that appears to substantially increase the hyperglycemia toxicity compared to breast cancer data, despite similarly requiring a baseline hemoglobin A1C of less than 8 percent. While these types of adverse reaction data are not unprecedented in oncology trials, the incidence and severity of toxicities that may be acceptable to patients is generally lower when the clinical benefit is modest.

In summary, the demonstrated improvement in rPFS was statistically significant, with a hazard ratio of 0.81, which is a modest treatment effect in the context of other results upon which FDA has granted previous approvals in mHSPC. The treatment

effect was supported by generally consistent results across sensitivity analyses, though the clinical meaningfulness of the findings remain uncertain.

We are concerned that the benefit-risk of the addition of capivasertib may not be favorable considering the clinical context. The enrolled population had early metastatic disease with a median time to progression or death of approximately 2 years. We note that the majority of patients with PTEN-deficient mHSPC had no or mild symptoms at baseline. In contrast, 71 percent of patients in the capivasertib arm had at least one grade 3 or higher adverse reaction.

Additionally, consider the clinical challenge that patients and providers will not be able to distinguish capivasertib benefit from abiraterone when evaluating benefit-risk for a given patient. This potential for overtreatment for years is different from monotherapy, where efficacy of a single agent can be more directly assessed. While this concern is true of any combination therapy, it is heightened here because of the long expected

duration of therapy, given the efficacy and safety of abiraterone.

In the absence of an improvement in OS and with the added toxicity of capivasertib, the activity of the control arm needs to be considered. While the control arm therapy of abiraterone doublet was acceptable from a regulatory perspective, guidelines and meta-analyses suggest that this is not the most preferred and active control arm therapy. This is a consideration in the clinical interpretation of the meaningfulness of the improvement of rPFS.

The combination of capivasertib plus abiraterone and prednisone or prednisolone resulted in substantially increased toxicity compared to placebo plus abiraterone. Increases in hyperglycemia events resulted in increased healthcare utilization, including insulin. More patients experienced fatal adverse reactions in the capivasertib arm, particularly in the first few months, while the expected OS in this population appears to be several years. Therefore, we ask the ODAC to consider the benefit-risk considered in CAPItello-281. After the

discussion, we will ask the committee to discuss and vote on this question.

Based on the CAPItello-281 results, does the benefit of adding capivasertib to abiraterone and prednisone outweigh the risk for the proposed indication? Thank you for your attention. I turn the meeting back over to the chair.

Open Public Hearing

DR. VASAN: Thank you. We will now begin the open public hearing session.

Both the FDA 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 relationship that you may have with the industry group. For example,

this financial information may include the industry group's payment of your travel, lodging, or other expenses in connection with your participation in the meeting.

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

The FDA and this committee place great importance 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 today. That said, and in any instances and for many topics, there will be a variety of opinions. One of our goals for today is that this open public hearing is to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect.

For those presenting virtually, please remember to unmute and turn on your camera when your OPH number is called. For those presenting in person, please step up to the podium when your OPH number is called. As a reminder, please speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, please state your name and any organization you are representing, for the record. You have five minutes.

DR. ZUCKERMAN: Thank you. I'm Dr. Diana Zuckerman, President of the National Center for Health Research. Our nonprofit research center does not accept funding from companies with a financial interest in our work, so we have no conflicts of interest.

Prior to my current position, I was a postdoc at Yale Medical School, conducted research at Harvard and Yale, and investigated FDA approval decisions for the U.S. Congress. On a personal note, my husband and my dad both were treated for prostate cancer, so I know the importance of your work today. And today,

I will focus on the most important question for the FDA and for patients: are the results clinically meaningful? I thank the FDA for focusing on that question, and I agree with the FDA review that the progression-free survival results represent a small treatment effect in the context of previous approvals demonstrating greater effects.

In CAPItello-281, the radiographic progression-free survival hazard ratio estimate, as you've heard, was 0.81, and that raises questions about whether the benefit is meaningful, especially since there was no statistically significant overall survival benefit at the interim analysis. And even for a short-term study, that lack of benefit is still important.

I kept in mind that the FDA told AstraZeneca in 2020 that the agency was concerned with the study design and had said that overall survival might be necessary to be significant in order to prove the benefit of this drug, because adding a new drug to an effective and well-tolerated therapy makes it difficult to determine the benefits of that

additional drug, as you all know. Had the difference in progression-free survival been more substantial, a significantly better overall survival might have been less important. However, the PFS showed a modest difference that was only significant at the 0.05 level, which is really about the minimum to be relevant for a clinical trial.

So, what about the risks? As you just heard, the addition of this drug resulted in increased serious toxicities, including early fatal adverse reactions, increased healthcare utilization, and worse patient-reported outcomes such as severe diarrhea and other symptoms that can really harm the quality of life.

As FDA noted, when the patients were enrolled in the study, most had no symptoms, or mild symptoms, and they could have expected two or three years without progression of cancer. That's why the adverse events were more problematic than they would have been for patients with more advanced disease. So we agree with the FDA that the risks of the drug seem to be questionable in terms of outweighing the

benefits.

And there are other shortcomings as well. Number one, the control arm therapy was not the triplet therapy that's currently preferred for these kinds of patients; number 2, the secondary endpoints were based on exploratory studies, so those data should not be used as the basis of an FDA approval. And the differences were, again, within the confidence intervals close to 1, and so they were not necessarily meaningful. To earn FDA approval, the magnitude of the treatment effect must be weighed against toxicity. The prior prognosis of this subgroup of patients does not -- I'm sorry. The poor prognosis does not, in and of itself, establish that a modest treatment effect is clinically meaningful.

In conclusion, I agree with the FDA's concerns that the demonstrated magnitude of improvement in PFS is not proven to be clinically meaningful given, number one, the absence of a benefit in overall survival; number two, the added toxicity, including increased number of early deaths; number three, the early metastatic disease state that

is being studied; and number four, and last, the lack of external data supporting meaningful efficacy of this drug, or of any AKT inhibitors in patients with this type of prostate cancer. Cancer patients deserve better. Thank you so much.

DR. VASAN: Thank you.

Speaker number 2, please state your name and any organization you are representing, for the record. You have five minutes.

DR. AGARWAL: Hi. My name is Dr. Neeraj Agarwal. I'm a medical oncologist specializing in prostate cancer and a clinical trialist. I practice at the Huntsman Cancer Institute at the University of Utah. I'm speaking today as an independent physician with no financial conflict of interest.

I would like to focus on one central question. Does capivasertib meaningfully improve outcomes for a clearly defined high-risk patient population with unmet need? And based on the data, my answer is yes. CAPItello-281 focuses on patients with PTEN-deficient metastatic hormone-sensitive prostate cancer, defined by 90 percent, or more, loss

of PTEN protein on immunohistochemistry.

This is a clinically aggressive group. PTEN loss activates the PIK3/AKT pathway, creating a parallel growth signal that is not suppressed by standard of care therapies. In practice, these patients progress faster, transition earlier to castration-resistant disease, and respond less well to standard therapy such as ADT plus ARPI. Other options such as docetaxel lack clear evidence of benefit in this specific patient population and have limited acceptability, with real-world data showing use in only 10 to 15 percent of patients in the U.S. in the castration-sensitive setting.

Even in this trial, if you look at the control arm, median radiographic progression-free survival, it was only 25.7 months, confirming poor outcome with standard of care therapies. This is a phase 3, biomarker-selected trial that met its primary endpoint. Median radiographic progression-free survival improved from 25.7 to 33.2 months, with a statistically significant hazard ratio of 0.81, as we heard. Importantly, the benefit

increases with greater PTEN loss, reinforcing a clear biological signal and supporting a precision oncology approach.

Beyond rPFS, multiple clinically meaningful secondary endpoints also favored capivasertib. Time to castration resistance and time to PSA progression are both improved. These are not just trial endpoints. Delaying the transition to castration-resistant prostate cancer, the symptomatic and ultimately lethal phase of disease, and delaying PSA progression, are outcomes that patients truly care about. These translate into more time feeling well, more time with family, and more time before facing the physical and emotional burden of advanced disease, which is castration-resistant disease. Delaying progression means delaying pain, fractures, and need for more toxic therapies. In simple terms, we are delaying the most difficult phase of prostate cancer.

The safety profile is manageable and consistent with expectations. Adverse events such as hyperglycemia, rash, and diarrhea are predictable,

occur early, and can be addressed with dose modification. Discontinuation rates remain relatively low, and the morbidity of progressive disease is far greater. Overall survival data are not yet mature, but the trend is favorable. Waiting for full maturity would delay access to a therapy that has a strong biological rationale and consistent benefit across multiple clinically meaningful outcomes.

At its core, this is about giving clinicians the ability to offer rational, targeted options to patients who currently face poor outcomes. We will select patients carefully, monitor toxicity closely, and use this therapy thoughtfully, but we need access in order to do that.

In summary, this is a high-risk, biomarker-defined population with clear unmet need. The trial met its primary endpoint. Secondary endpoints reinforce benefit, and the safety profile is manageable. Most importantly, this therapy offers a real opportunity to delay progression and reduce suffering. For our patients, time matters, time

without pain, without castration- resistant disease, without progression, and time with dignity. And I think capivasertib helped give them more of this time in this trial, so I strongly urge the committee to support its approval. Thank you.

DR. VASAN: Thank you.

Speaker number 3, please state your name and any organization you are representing, for the record. You have five minutes.

DR. PHILBIN: Hi. My name is Mike Philbin. I represent FORCE. FORCE is a national nonprofit organization that supports and represents individuals and families affected by hereditary cancer, so I'm here to give a hereditary prostate cancer patient perspective.

I'm a retired organic chemist. I'm a 12-year hereditary prostate cancer survivor. Myself, my father, both my brothers are all diagnosed with clinically significant prostate cancer. My father and one of my brothers had metastatic disease and died from the disease, so clinically significant prostate cancer is 100 percent in my family. I was

diagnosed with the BRCA2, B-R-C-A-2, mutation germline back in 2020, and I've already stated I volunteer with FORCE since 2021.

I'm very aware of all the different cancers now. Men with inherited germline mutations and DNA repair genes, such as BRCA2 or ATM, are more likely to develop prostate cancer at a younger age. I was 52. My dad was 55. It was de novo metastatic. He died two years later. They're more likely to have high-grade or metastatic prostate cancer -- my dad and my brother both metastatic -- more likely to have aggressive progression and poorer outcomes.

Published data suggest 5 to 10 percent of men with prostate cancer have an inherited germline mutation. And I think it's somewhere in the order of 1 in 300 men actually have an inherited germline mutation, yet 5 to 10 percent have prostate cancer, and even a higher proportion in terms of high-grade metastatic prostate cancer.

Men with inherited prostate cancer mutations are already underserved by current screening guidelines. I started screening at 40 despite what

the screening guidelines were. I was diagnosed at 52, and my cancer was caught early, and I've been no evidence of disease since 2014. But a lot of men, treatment options will remain limited, and outcomes are too poor because they're getting diagnosed when the disease has spread.

So I'm an organic chemist, so I'm going to pronounce it as capi-vasertib, is how I would pronounce it. So why it matters for patients. Many men with advanced prostate cancer have PTEN loss. The problem with these tumors is they're dealing with higher risk prostate cancer with higher Gleason scores, metastatic disease, and then cancer that keeps growing quickly even after starting usual treatments.

The CAPItello-281 trial, to see if adding capivasertib to standard treatment ADT with androgen synthesis inhibitors, could help men with metastatic hormone-sensitive prostate cancer with PTEN loss. The results show the combination helped men go longer before the cancer clearly worsened on scans, the group receiving capivasertib at 7-and-a-half months

on average.

I volunteered a lot of people with various metastatic diseases, and I can tell you, when you're told that your scan shows that your tumors are stable and not growing, that gives people hope. So that's outside of overall survival and the rest of the stuff. But as a patient, when you're living day in and day out with your scans and seeing what's happened, to hear that your scan is not progressing is a huge thing for a patient to hear.

Targeted therapies like capivasertib represent an essential step forward in precision oncology, not just treating prostate cancer broadly, but also treating the molecular drivers of aggressive disease. As a FORCE volunteer on behalf of the FORCE community, patients, and families, and caregivers who live with hereditary cancer risk, I want to emphasize the broader point. People impacted by cancer need timely access to evidence-based treatment options that can extend life and help people live better when strong clinical data show a meaningful benefit for a clearly defined group of patients. FORCE supports

making those options available so patients and their doctors can make informed choices.

The evidence addresses the important unmet need for men with aggressive forms of prostate cancer, shows a clinically meaningful benefit, a clearly defined high-risk population, reflects risk-benefit balance for patients and clinicians, and can reasonably consider in the setting.

And finally, first, I want to thank all of you. I should have done that first. I respectfully ask the committee to keep the patient perspective at the center of today's discussion -- that goes without saying -- and support regulatory decisions that are guided by the best available evidence, especially when the evidence points to a meaningful benefit for a subgroup of patients with limited options. Patients deserve both scientific rigor and a sense of urgency because delays in access can translate to real harms for individuals and families. Thank you for considering the patient voice today.

DR. VASAN: Thank you.

Speaker number 4, please state your name and

any organization you're representing, for the record. You have five minutes.

DR. SHORE: Yes. Hi. Apologies. I was having challenges with the mute. Hi. I'm Neal Shore. I'm the Medical Director for GU Oncology at START CANCER RESEARCH. My research site, where I've been for the last 30 years of my career, is in Myrtle Beach, South Carolina. I've done over 500 clinical trials. About 90 percent of them have been in GU oncology.

It's a great pleasure to address this very important ODAC today. I have no financial relationship, nor any compensation for presenting my thoughts today. I'm actually here at the Advanced Prostate Cancer Consensus Conference, which meets every two years to discuss and debate unmet needs in prostate cancer. So I'm overseas and wouldn't want to miss this opportunity.

I participated in two separate phase 3 PIK3/AKT pathway therapeutic trials, one in mCRPC, and then I've had the pleasure to be part of the CAPItello-281. And frankly, I've always been

fascinated and very enthusiastic at biomarker-directed trials, regardless of the type of marker, whether it's blood based, tissue based, urine based, whether it's immunohistochemistry or NGS. In this particular case, I want to focus a little bit on the IHC aspect and not be repetitive to the great comments I've already heard today.

I've also participated and authored many publications on the importance of NGS testing for HRR alterations to help us guide therapeutic options both as monotherapy and in combination therapies. This is how we will make cancer care -- not just in prostate cancer but across the board -- less of a one-size-fits-all and more truly precision based, personalized, whatever your favorite adjective is, tailor based. I think this is clearly what patients want. It's what physicians want.

In 2026, there's a marked underutilization of biomarker testing for prostate cancer patients. I just think that the combination of finding, now in CAPItello-281, that this very scalable, very teachable to community pathologists, not just

academic medical centers, where it's very scalable and very economic, this can be done. And this, basically, will further allow patients and physicians to undergo this very vaunted but important concept of shared decision making.

Yes, there are some added toxicity. That's added toxicity to whether we go to a doublet or a triplet, or perhaps even in the future, we'll have quadruplets for the right patient, right therapy, understanding what their comorbidities are, understanding that it's the biology that really matters now more than anything else as opposed to the also important aspects of tumor volume and tumor location.

So I established IHC PTEN loss testing when I first did a potential trial, and I routinely get it. I've had different community-based pathologists who regularly perform the treatment or the investigation, and I've also worked with industry colleagues, whether it's been in Foundation Medicine, Caris, or Tempus, and I've asked them to get it as well. And that's not been challenging, but what it does do is

it informs me.

I've also provided docetaxel as a uro oncologist since 2007. I routinely use it. But as has already been stated, and I'm sure you've heard this, it's not particularly well accepted by patients. And for patients who require it, or at least were offered, a very small single-digit percentage typically want to take that. Now, there's no biomarker per se that lends itself to using docetaxel in the mHSPC space. The biology here for IHC PTEN greater than 90 percent deficiency has clearly been demonstrated.

As I said earlier, cancer care is assuredly no longer a one-size-fits-all. Understanding what someone's germline, somatic, HRR, TMB high, MSI high, and now PTEN loss, HER2 loss on IHC as well, this allows for the opportunity to expand that very important conversation with patients to say, you have a unique set of a biomarkers, or markers, where we can leverage that, and we could potentially improve your outcome.

Delay progression. Patients really enjoy

delay of progression. In my experience, very few come in to me and actually say how long do I actually have to live? What is my survival? We understand the importance of research and trials, of course, of the binary component of overall survival. It's been somewhat of the gold standard for years and years in prostate cancer, not so in many other solid tumors. But if we can delay disease, if we can delay the onset, the need for another antineoplastic discussion, and we don't obviate the use of other approved therapies, which is the case in the CAPItello-281 study, then we've done the patient a service by delaying the onset to resistant disease biology, delaying onset of skeletal-related events, which has clearly been demonstrated in CAPI-281.

So I think these are really important concepts. It's evolved in the way I treat patients. I really focus on the biology now as the number one aspect of importance, in addition to all the other things that we typically look at, both the volume of disease, location, patient preference, and having the ability to have that shared decision making

conversation. We talk about this.

DR. VASAN: I'm sorry to interrupt. We're actually at time. Would you be able to just please sum up in five seconds?

DR. SHORE: Yes. My apologies. I would just say that it's been a great pleasure to address this to this ODAC panel. Thank you very much. I strongly express my desire, so I hope you vote favorably for its approval. Thank you.

DR. VASAN: Thank you.

Speaker number 5, please state your name and any organization you are representing, for the record. You have five minutes.

MS. CARITHERS: Hello. Thank you. I'm Gina Carithers. I am here as the President and CEO of the Prostate Cancer Foundation. We have no financial relationship in our attendance here today with AstraZeneca. Therefore, I have no conflicts related to this testimony. On behalf of millions of patients, their families that the Prostate Cancer Foundation serves, I'm speaking with you today to express our unequivocal support that the FDA approve

this therapy as a targeted therapy. And you've heard this a little bit. It's really essential for men who have PTEN deficiency, that we can treat them specifically.

I'll provide a little bit of background on the Prostate Cancer Foundation. We are founded in 1993. We've invested over a billion dollars in prostate cancer research, and we're invested heavily in research to develop scientists across this country and the globe who can understand prostate cancer, the biology, and further its development of treatments to the marketplace. We've been involved in 14 FDA-approved treatments, at least in the seeding component of those trials. We haven't been involved in this particular product development.

We are here today to look at the next steps by addressing the stark unmet need faced by patients specifically with PTEN-deficient metastatic hormone-sensitive prostate cancer. PTEN deficiency is actually common in metastatic hormone-sensitive prostate cancer. These patients are diagnosed with de novo disease, having no prior treatment, and the

biology of this disease presents a high risk for these men and a shorter time to death. They also benefit less from the standard of care treatment that we've come to rely on in the next-generation hormone therapies. They experience shorter progression-free survival, overall survival, and they also get quicker onset of skeletal-related events and other consequences of a progressive disease.

Upon the onset of castrate resistance, many develop these painful skeletal metastases and experience the morbidity and mortality that come from fractures, and have other poor, near-term outcomes, which is why we invest so heavily in evaluating targeted therapies in the era we're in with science and technology today.

Studies clearly show that PTEN is an actionable biomarker. And as you know, capivasertib can target PTEN-deficient tumors by acting as a potent pan-AKT inhibitor that blocks downstream signaling, hyperactivation, resulting from PTEN loss. In the phase 3 CAPItello-281 trial of patients with PTEN-deficient mHSPC, adding capivasertib to the

standard of care, abiraterone acetate, prednisone, and ADT, significantly prolonged radiographic progression-free survival in that primary endpoint analysis.

This delays the onset of castrate-resistant disease, where in these men, we see it much more rapid than we do our traditional men with metastatic hormone-sensitive prostate cancer without PTEN deficiency or other genetic predisposing factors. These benefits are meaningful for the patient who face a short treatment option.

I recently have navigated a man who has this deficiency, a PTEN deficiency, and sitting listening to the medical oncologists having to help that patient understand that his time to progression is necessarily less than otherwise could be projected is a very difficult conversation to listen to. The benefits are meaningful for the patient who face that shortage of treatment options. They represent a world of difference. The need for these patients is urgent, and targeted treatment such as capivasertib plus abi, plus prednisone and ADT, it offers an

evidence-based actionable hope. Approving this first-in-class precision combination is how we can deliver that hope to men today.

In addition, the laboratory test to assess PTEN deficiency is well established. It's widely available and scalable. Immunohistochemistry for PTEN detection is used routinely in breast cancer and can readily be applied to the physicians in the community, as well as in academic centers across the United States. Patients and family tell us how much access would mean to them.

Patients with PTEN-deficient metastatic hormone-sensitive prostate cancer deserve hope, not frustration, and the urgency is clear to act. This is a strong rationale and a solution within reach. The Prostate Cancer Foundation's deep understanding of prostate cancer disease biology, the molecular mechanisms underlying PTEN-deficient forms of mHSPC, and other careful review of the CAPItello-281 trial design, the conduct, the results, make us confident that capivasertib plus ADT and abiraterone can offer an essential new treatment to men who are at this

high-risk, high-need category today. And at the heart of everything we do are the men and the families we serve throughout the United States and the world. It is on our behalf, we respectfully urge for your favorable consideration. Thank you.

DR. VASAN: Thank you.

Speaker number 6, please state your name and any organization you were representing, for the record. You have five minutes.

MS. BUGLER: Good afternoon, everyone. My name is Courtney Bugler, and I'm the President and CEO of ZERO Prostate Cancer. I am also a 20-year cancer survivor myself and patient advocate, and I joined ZERO for my dad who is living with prostate cancer himself. And while the applicant has funded some of our work in the past, we have no financial interest in this discussion today, and I have not been personally compensated.

ZERO is the voice for the prostate cancer community. We are the number one provider for programs, services, and resources for prostate cancer patients and those at risk. We have things like

150 support groups around the country, a ZERO 360 patient assistance line, advocacy programs, patient navigation, and as of this morning, the first ever AI-enabled, text-based education and support tool.

We are not here to advocate for or against the recommendation that the body will make today. That is not our role here. However, we have read the briefing documents carefully, and we understand the scientific and regulatory questions at stake. I'm here to ask you to consider something that doesn't always appear clearly in clinical trial data, the lived experiences of patients whose lives hang in the balance of your deliberations today. Each data point is a person, a person with traditionally worse outcomes who is begging for options.

Let me tell you about Michael. Michael was 52 when he was diagnosed with mHSPC. Michael is like so many with the disease, people with jobs, children, grandchildren, but he is also part of a patient population that is PTEN deficient. And when he found out, what he did was what so many patients do. They went home and they searched online. Patients who do

that search find some scary numbers. PTEN loss is associated with more aggressive disease and poorer outcomes. They learn their cancer might not respond as well to standard therapies, and they learn there aren't many therapies specifically designed for their tumors.

The FDA asks whether rPFS improvement is clinically meaningful in the absence of an effective overall survival, but I want to explain what delaying progression means to the patients that we serve every day at ZERO. When a patient's disease converts from hormone sensitive to hormone resistant, everything changes. It's a turning point. Treatment options become more limited and more toxic, and the future becomes uncertain, and the clock starts ticking faster. Every month a patient remains in the hormone-sensitive state is a month of better function and more hope. That's not just a clinical endpoint. It's time with family, time at work, time living rather than just surviving, more access to salaries and families that keep them going.

The FDA notes that median OS is measured in

years in this population as if that diminishes the value of delaying progression, but we would argue the opposite. Because those patients have years ahead of them, the quality of those years matter enormously. The FDA acknowledges that PTEN deficiency is associated with poor prognosis but then dismisses the therapeutic implications, saying poor prognosis does not alter the FDA's benefit-risk framework.

The framework being used to evaluate this treatment may not fully reflect what matters most to patients. From a patient perspective, this is backwards. Men with PTEN-deficient disease have worse outcomes with standard therapy. And as we have heard by others so far, they are not accessing that triplet therapy that some might argue we should be comparing this against. They are the ones who are calling our ZERO 360 patient assistant line asking, what else can we do?

The potential approval that you are discussing today is the next step in precision medicine for prostate cancer and a modern therapy grounded in targeting specific molecular pathways.

It is a first-in-class opportunity.

Let me be clear. We're not here to approve the approval or the denial. That's your decision to make based on the evidence. But we do ask that you review the data today and you center the patient experience. Consider not just the statistical outcomes, but what these outcomes mean for real people living with this disease.

When you weigh the benefits of this treatment, please consider the following: What delay progression means in human terms, months or years of quality of life before disease worsens and before treatment options can become even more limited and more toxic. How patients actually experience and manage side effects with their doctors and what treatment choices patients would make for themselves, not necessarily what the most active therapy is in theory, and the value of options, especially for a first-in-class therapy.

The FDA asks in its voting question, does the benefit of adding this to abiraterone and prednisone outweigh the risk? I would ask you to consider a

parallel question. For which patients might that answer be yes? And should those patients have the opportunity to make that choice with their doctors? Thank you.

DR. VASAN: Thank you.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience.

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 industry's non-employee presenters, to advise the committee of any financial relationships that they may have with industry, such as consulting fees, travel expenses, honoraria, and interest 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 will now proceed with the presentations from AstraZeneca.

Applicant Presentation - Andrew Foxley

DR. FOXLEY: Good afternoon. My name is Andrew Foxley, and I'm the Late Development Franchise Head for Oncology Small Molecules at AstraZeneca. I've been involved in the development of capivasertib since its discovery in 2009, and for the last six years have served as the global lead for its late-stage development.

Capivasertib is a first-in-class inhibitor that was approved by the FDA in November 2023 for the treatment of HR-positive HER2-negative PIK3CA/AKT1 or PTEN-altered metastatic breast cancer. Today, we

will review the positive phase 3 data for capivasertib in PTEN-deficient metastatic hormone-sensitive prostate cancer or mHSPC.

39,000 men are diagnosed with mHSPC in the United States each year. Of these, 25 percent have what we refer to as PTEN-deficient mHSPC. These tumors lack PTEN protein expression in at least 90 percent of tumor cells. This indicates a loss of function of the PTEN tumor suppressor. Real-world evidence indicates that patients with PTEN-deficient mHSPC have poorer prognosis and increased risk of mortality. This population was the focus of CAPItello-281.

In PTEN-proficient cancer cells, androgen receptor signaling is the primary driver of proliferation. This can be limited by current androgen deprivation regimens. In these cells, the PI3-kinase/AKT pathway is largely naturally suppressed by PTEN. However, in PTEN-deficient cells, loss of PTEN function results in activation of the PI3-kinase/AKT pathway and becomes an independent additional driver of proliferation that is not

addressed by current therapeutic approaches. Capivasertib's mechanism of action compensates for the loss of PTEN function by inhibiting the AKT node of the activated PI3K/AKT pathway. This reduces proliferation and delays disease progression to prolong the time that patients can benefit from continued androgen deprivation therapy.

CAPItello-281 is the first pivotal study to prospectively enroll a PTEN-deficient mHSPC population. For this study, we made three strategic design choices. First, we drew proof of concept from a small phase 2 trial of ipatasertib, another AKT inhibitor given in combination with abiraterone in castration-resistant disease. The specified primary analysis in the group with 90 percent PTEN loss showed an rPFS hazard ratio of 0.39 versus 0.84 for those with PTEN-proficient tumors.

An exploratory analysis later found that a cutoff IHC equivalent to 50 percent was less discriminative. Ipatasertib moved forward into phase 3 in an unselected metastatic castration-resistant prostate cancer population. The

prespecified co-primary endpoint for that phase 3 was rPFS in the population with 50 percent PTEN deficiency. We chose to apply a 90 percent cutoff to ensure near complete loss of PTEN. Second, and in another difference from ipatasertib, we studied mHSPC rather than castrate-resistant disease because PTEN deficiency arises early in the disease course. Third, we paired with abiraterone because enzalutamide adversely affects the pharmacokinetics of capivasertib.

We initiated CAPItello-281 in 2020 after consultation with the FDA. The primary analysis was performed in October 2024, and after careful review of the data, we filed a supplemental new drug application in August 2025. A day 120 safety update was provided in December 2025, and this added 9 months of additional safety follow-up.

Given the totality of the evidence that we will discuss today, we are proposing that capivasertib should be approved in combination with abiraterone for the treatment of adult patients with metastatic hormone-sensitive prostate cancer that is

PTEN deficient as detected by an FDA-approved test. The agency has asked you to consider whether the benefits of this therapy outweigh the risks for patients with PTEN-deficient mHSPC. Data from the primary endpoint and key secondary endpoints demonstrate the benefits of capivasertib in delaying progression of this high-risk form of prostate cancer.

As an add-on therapy, we recognize that capivasertib brings additional adverse events. We have examined the safety data carefully. The majority of these events can be predicted and managed with established strategies, and these have been developed from our extensive experience with our approved indication for capivasertib in breast cancer. We agree that there is some impact on patient-reported symptoms. However, we see limited impact on functional well-being scores. And importantly, the majority of patients reported either no or low bother from side effects. Overall, the risk-benefit balance is in favor of allowing patients with this biomarker selected and aggressive form of

prostate cancer to have the option of treatment with capivasertib.

Here, you can see the presenters for the remainder of our presentations. Dr. Elisabeth Heath from the Mayo Clinic will discuss the disease background and unmet need. Drs. Gaia Schiavon and Mayur Patel from AstraZeneca will present our efficacy, safety, and patient-reported outcome results. Finally, Dr. Daniel George from the Duke Cancer Institute will provide his perspective on the potential use of capivasertib in clinical practice. We also have Drs. Lotan, Oliveira, and Rugo with us today to respond to your questions.

Thank you. And now I'd like to invite Dr. Heath to the podium.

Applicant Presentation - Elisabeth Heath

DR. HEATH: Good afternoon. My name is Dr. Elisabeth Heath, and I serve as Chair of the Department of Oncology at the Mayo Clinic. I am a genitourinary medical oncologist and clinical investigator who has cared for men with prostate cancer for more than 25 years and have conducted

clinical and translational research focused on understanding the biology of this disease and improving patient outcomes.

I'd like to begin by noting that I have no personal financial interest in the outcome of the data being discussed today. Any compensation associated with my participation in this presentation is provided to my institution rather than to me personally. My remarks today reflect my clinical experience caring for patients with advanced prostate cancer, as well as my interpretation of the scientific evidence in this field.

Despite major advances in prostate cancer treatment over the past decade, many men with metastatic prostate cancer continue to experience aggressive tumor biology that is not fully addressed by current therapies. Clinically, the disease progresses from localized to mHSPC, and ultimately metastatic castration-resistant prostate cancer, which is lethal. Upon development of castration-resistant disease, care becomes more complex, requiring additional therapies, monitoring,

and greater symptom burden. At this stage, patients experience rapidly worsening disease that is difficult to control, with painful bone involvement and increased urinary symptoms.

Today, I will focus on mHSPC, metastatic disease that is still responsive to hormone therapy. While not curable, it is generally highly treatable. For clinicians, this is a critical window in the patient's journey, where treatment choices aim to delay progression to castration-resistant disease.

Over the past decade, the treatment landscape has evolved substantially with the introduction of treatment intensification strategies. Today, ADT is commonly combined with androgen receptor pathway inhibitors, or ARPIs, and doublet regimens that are widely used in clinical practice. Triplet strategies that add docetaxel-based chemotherapy are available for high-volume patients, but their use remains low.

Treatment decisions today are largely guided by disease burden and risk classifications determined by the presence or absence of visceral metastases, the number of bone metastases, and the Gleason score.

Patients with high-volume or high-risk disease generally have poorer outcomes. Once treatment begins, we monitor patients' progress by evaluating their clinical symptoms and by measuring prostate-specific antigen levels, also known as PSA, which is reflective of androgen receptor activity.

As our understanding of prostate cancer biology has evolved, it has become increasingly clear that metastatic prostate cancer represents a collection of biologically distinct subtypes. Our treatment paradigm is now evolving towards a biomarker-directed treatment. For example, patients with BRCA2 mutations can now receive niraparib. The next most obvious opportunity for biomarker-directed treatment is the 25 percent of patients who have tumors that are PTEN deficient.

We can readily identify PTEN-deficient tumors using immunohistochemistry, which evaluate cytoplasmic PTEN protein expression in tumor cells. Tumors are considered PTEN proficient when cytoplasmic staining is preserved and PTEN deficient when there is near complete loss of staining across

tumor cells. One advantage of immunohistochemistry is that it directly measures functional loss of PTEN protein expression, which may not always be fully captured by genomic testing alone. In addition, immunohistochemistry is widely available in clinical pathology laboratories and represents a practical approach for identifying patients whose tumors demonstrate PTEN deficiency.

This population faces significant unmet need. Patients with PTEN-deficient tumors have a worse prognosis because of their more aggressive disease biology. In real-world studies, patients with PTEN-deficient mHSPC had a shorter time to progression to castration-resistant disease compared to patients with intact PTEN.

Importantly, the poorer prognosis for PTEN-deficient mHSPC is evident even in patients who typically would be considered low risk based on traditional risk factors, and this faster progression unfortunately impacts survival. Four real-world survival outcomes were observed in patients with PTEN-deficient mHSPC when treated with standard of

care therapies compared with patients whose tumors retain PTEN function. These data support that targeted therapies are necessary to adequately treat these patients.

In summary, patients with PTEN-deficient mHSPC experience faster disease progression and a shorter life expectancy. Despite advances in treatment landscape for mHSPC, standard of care options are inadequate for patients with this tumor biology. This is because PTEN deficiency leads to activation of the PI3-kinase/AKT signaling pathway, a critical independent oncogenic driver that accelerates progression.

Here, we have an identifiable and actionable biologically-defined population who we know have worse outcomes. These patients can benefit from targeted treatment intensification as early as possible in their disease course. Adding AKT inhibition to androgen receptor pathway inhibition is an opportunity to improve outcomes for patients with PTEN-deficient mHSPC. The remainder of today's discussion will focus on this strategy.

Thank you. Now, I would like to invite Dr. Schiavon to the podium.

Applicant Presentation - Gaia Schiavon

DR. SCHIAVON: Thank you, Dr. Heath.

My name is Gaia Schiavon. I'm a Medical Oncologist and Global Clinical Head at AstraZeneca. It's a pleasure to present the clinical efficacy outcomes data for CAPItello-281.

CAPItello-281 is the first pivotal phase 3 study, enrolling patients with newly diagnosed PTEN-deficient mHSPC. Patients were allowed to have received up to 3 months of prior androgen deprivation therapy, plus or minus abiraterone, and a background of prednisolone or prednisone. Patients with high- and low-risk disease were eligible. The study excluded patients with type 1 diabetes, type 2 diabetes requiring insulin, and those with HbA1C of 8 percent or higher, which is the target recommended by the American Association of Diabetes for older patients with multiple chronic illnesses, including cancer.

1,012 patients were randomized 1 to 1 to

treatment with abiraterone and ADT, plus either capivasertib or placebo, all at standard approved doses. Capivasertib was administered 4 days on, 3 days off as approved in breast cancer. This intermittent schedule was chosen in early-phase trials based on tolerability and the degree of target inhibition. Following discussion with the agency, the primary endpoint was set at investigator-assessed radiographic progression-free survival, or rPFS, a well-established and validated primary endpoint in prostate cancer.

We will share today a number of efficacy analyses looking at endpoints widely adopted in prostate cancer clinical studies, including overall survival. The key inclusion criterion for this study was PTEN deficiency. PTEN status was prospectively determined using central testing with a validated immunohistochemistry assay. IHC was chosen for its low failure rate and its ability to detect the absence of PTEN protein. Pathologists assigned a percentage score of tumor cells with no cytoplasmic staining. This histogram is showing the distribution

of PTEN scoring within the screened population.

PTEN deficiency was defined by at least 90 percent of tumor cells with no staining, which was identified in 25 percent of patients. As expected, IHC had a very high success rate in 25 percent of patients at PTEN-deficient tumors. This resulted in about 1500 patients moving to the next step of screening and 1,012 patients randomized in the study.

Today, I will be presenting the results of the primary analysis, which was based on the data cutoff in October 2024 at 39 percent maturity with a median rPFS follow-up of approximately 18 months. The overall survival final analysis will be triggered by 522 deaths and is expected at the end of 2027.

The statistical design employed a multiple testing procedure, which followed a simple hierarchy. The two-sided 5 percent alpha is assigned entirely to the primary endpoint, rPFS, then that is cascaded to OS as the first key secondary endpoint, and in turn to the other key secondary endpoints as illustrated. Of note, the plan was to analyze the endpoints below OS, even if OS did not achieve statistical

significance at the primary analysis.

Baseline patient demographics and disease characteristics were balanced overall between the treatment arms across age, race, and measures of disease severity. Although the majority of patients were classified as high risk and high volume of disease, and notably 19 at visceral disease, more than a third of patients were low risk. Low-risk status is usually associated with less aggressive disease and a better prognosis. However, the data that we will share today show that PTEN deficiency can exist independently of traditional prostate cancer risk factors and is associated with poor prognosis. I will come back to this point shortly.

Now let's look at the results of CAPItello-281. The study met its primary endpoint. Capivasertib added to abiraterone led to a statistically significant improvement in radiographic progression-free survival as measured by investigator assessment. The hazard ratio was 0.81. The median rPFS increased from 25.7 to 33.2 months, giving a clinically meaningful 7.5-month benefit. I'd like to

point out that the control arm performed markedly poorly, further demonstrating the extent of unmet need of this PTEN-deficient mHSPC population.

We conducted several preplanned sensitivity analyses of rPFS to assess the robustness of this endpoint. This included blinded independent central review or BICR. They collectively demonstrated consistency with the primary analyses by investigator assessment. Furthermore, you will see from the briefing document that the FDA has included further sensitivity analyses whilst also concluding consistency with the primary results.

Prespecified analyses in clinically relevant subgroups also showed the broadly consistent treatment effect in favor of capivasertib. As expected for small subgroups, we see wide confidence intervals. However, the rPFS hazard ratio for the majority of subgroups lies within the 95 percent confidence intervals of the primary rPFS analysis, supporting consistent benefit. The interim analysis of overall survival shows a hazard ratio of 0.9 favoring capivasertib, which is consistent with no

detriment at this time. At 26 percent maturity, approximately half of the patients were still receiving study treatment. Further follow-up is ongoing. Notably in the day 120 safety update, capturing an additional 9-month follow-up since the primary rPFS analysis, we see that 50 of the 77 new deaths were in the placebo arm.

In addition to the final rPFS and interim OS analysis, we will now present other endpoints that are considered most impactful in clinical practice. As you heard from Dr. Heath, these endpoints represent the major goals of treatment for patients and physicians. Symptomatic skeletal event-free survival is a composite endpoint including radiation therapy, new symptomatic pathological bone fractures, spinal cord compression, surgery for bone metastases, or death. Time to castration resistance, a critical inflection point for this disease, includes radiographic progression, PSA progression, and skeletal events. Finally, time to first subsequent chemotherapy indicates the time from randomization to the start date of subsequent chemotherapy or death,

which is important, as chemotherapy is associated with a marked decrease in quality of life.

First, let's look at symptomatic skeletal event-free survival. There is a meaningful treatment effect observed with capivasertib. We saw a hazard ratio of 0.82, meaning that patients treated with capivasertib experienced fewer and delayed symptomatic skeletal events. These include new symptomatic pathological bone fractures and spinal cord compressions, which often require surgical intervention. These events are associated with significant pain and morbidity and are a major challenge for patients.

I'm now going to show you two endpoints that drive treatment decision making. First is PSA progression, also known as biochemical progression. Capivasertib decreased the risk of PSA progression by 27 percent. Traditionally, we would expect PSA progression to drive castration-resistant events, but that is not what we see in this study. Looking now at the composite endpoint of time to castration resistance, which includes PSA progression,

capivasertib reduced the risk by 23 percent. However, you can see that there were more than double the number of castration-resistant events compared to the PSA progression events. This means a large proportion of patients enrolled in CAPItello-281 had radiographic progression or a skeletal event in absence of biochemical progression.

Treatment with capivasertib does not limit patient's ability to receive subsequent therapy. At this cutoff, about half of the patients were still receiving study treatment. As expected, a number of patients in the placebo arm, higher number, had progressed, and those received subsequent therapy. Cytotoxic chemotherapy was the most common, 80 percent of patients in the placebo arm compared with 66 in the capivasertib arm.

For those patients who discontinued study treatment due to radiographic disease progression and then received subsequent therapy, the use of chemotherapy was balanced between the arms. This suggests that treatment with capivasertib does not limit the opportunity to use chemotherapy later in

the patient's treatment course.

As expected with delay progression, capivasertib prolonged the time to subsequent chemotherapy. This prespecified exploratory endpoint showed a hazard ratio of 0.79 and a meaningful 13-month delay to the start of chemotherapy and its associated risks.

In summary, CAPItello-281 was a well-conducted phase 3 clinical trial that showed improvements in endpoints that relate directly to the patient's clinical experience and the way their disease is managed in the clinic. Taken together, the data demonstrate the consistently meaningful impact of capivasertib in altering the disease trajectory by slowing down disease progression and the development of symptomatic skeletal events, and by delaying the time to treatment changes, including chemotherapy. These benefits were obtained with no indication of overall survival detriment at this time, and follow-up for overall survival continues.

With this, I'd like to conclude and pass on to my colleague Dr. Patel.

Applicant Presentation - Mayur Patel

DR. PATEL: Thank you, Dr. Schiavon.

My name is Mayur Patel, and I'm the Vice President for Oncology Patient Safety at AstraZeneca. I will present the safety data from the CAPItello-281 trial, where capivasertib was added to abiraterone androgen deprivation therapy and prednisone in metastatic hormone-sensitive prostate cancer.

The safety profile of capivasertib is well characterized, with 3300 patients treated in clinical trials and over 6,000 patient-years of postmarketing exposure since its approval in breast cancer. Clinicians are familiar with this product and the strategies for monitoring and treating key on-target events of the AKT pathway, including rash, diarrhea, and hyperglycemia.

The approved combination of abiraterone, ADT, and prednisone is associated with cardiometabolic effects, infections, and hepatotoxicity. The safety profile in the CAPItello-281 trial was generally consistent with the known risks when combining these treatments. It is important to consider these risks

in the context of the poorer prognosis and the lack of targeted therapies for patients with PTEN-deficient metastatic hormone-sensitive prostate cancer. We will focus on the primary analysis set and conclude with the day 120 safety update.

Treatment duration of capivasertib was shorter than placebo, as adverse events in the capivasertib arm were managed with dose interruptions, reductions, and treatment discontinuation as needed. The relative dose intensity and the percentage of intended dose were high across both arms, with treatment durations ranging up to nearly 4 years in the capivasertib arm. This indicates that patients were generally able to receive treatment until progression. Importantly, the addition of capivasertib did not compromise exposure to abiraterone.

Over 90 percent of patients in both arms experienced an adverse event of any grade. Capivasertib increased the overall incidence of serious adverse events and grade 3 and higher adverse events compared to placebo. There was a small

numerical imbalance in adverse events with an outcome of death, 36 patients in the capivasertib arm and 26 in the placebo arm. Dose interruptions and reductions were utilized to effectively manage capivasertib adverse events.

Treatment discontinuation of capivasertib occurred early in the study. In most instances, patients were able to remain on abiraterone. The rate of discontinuation is consistent when adding a targeted therapy to standard of care backbone, as observed in the AMPLITUDE study. Nearly two-thirds of the discontinuations due to adverse events occurred in the first 3 months of treatment and stabilized thereafter. This indicates adverse event management is important to enable patients to stay on therapy.

There were more all-cause deaths in the placebo arm than in the capivasertib arm, underscoring the severity and the nature of the disease in this high-risk metastatic hormone-sensitive prostate cancer population. Using the primary data cutoff, there was a numerical

imbalance in the adverse events with an outcome of death. Fatal adverse events were distributed across multiple system organ classes. There was an early imbalance in deaths reported in infections, particularly sepsis. Across the entire study treatment period, fatal adverse events within the infections and infestations system organ class were balanced between the arms.

After a careful review of these early events in both groups, most were attributed to comorbidities in this population. Importantly, in the capivasertib arm, investigators assessed that 30 of the 36 overall deaths were not related to capivasertib. This reflects the challenges of establishing a cause of death in a population with significant comorbidities.

Now turning to these serious adverse events, about 40 percent of patients on the capivasertib arm, and approximately a quarter of patients on the placebo arm, experienced a serious adverse event. Infection events were the most common serious adverse events in both arms. Pneumonia was the most frequently reported and events observed in prostate

cancer patients, including urinary tract infection and urosepsis. Other serious adverse events were those associated with AKT inhibition: rash, diarrhea, hyperglycemia, and complications like diabetic ketoacidosis, which was precipitated by patients' underlying conditions.

The majority of adverse events in both arms were grade 1 and 2, as illustrated by the lighter segment of each bar, capivasertib on the left and placebo on the right. The most common adverse events in the capivasertib arm were diarrhea, hyperglycemia, and rash. In the placebo arm, you see adverse events commonly associated with abiraterone: hypertension, hot flush, and transaminase increases. Despite the occurrence of adverse events, there were no clinically meaningful differences between the groups in patients' functional or physical well-being.

We'll now shift to a detailed characterization of the three key capivasertib adverse events starting with rash. Rash presented here uses the prospectively defined group terms associated with AKT related rash. FDA has used the

more extensive list, including symptoms like dry skin and pruritis that may not be attributed to rash. Rash incidence in this trial was similar to the breast cancer population previously studied. Rash occurred early with a median onset time of 2 weeks, and two-thirds of the events were grade 1 and 2. Events were treated with antihistamines, topical steroids, and systemic steroids in most patients with grade 3 events. Rash led to discontinuation in about 5 percent of patients, and nearly 90 percent of events were reported as recovered or recovering at the data cutoff.

Diarrhea was reported in 52 percent of patients, less than what was observed in the breast cancer population. Diarrhea often occurred during the four dosing days, resolving during the three off days. It peaked early in treatment with a median onset time of around 2 weeks. Nearly 90 percent of diarrhea events were grade 1 and 2, and most patients reported 1 to 2 adverse events. Patients self-managed these events with loperamide. Discontinuations were infrequent, occurring in

5 patients, four of whom remain on abiraterone. Similar to rash, at the last data cutoff, more than 80 percent of patients with diarrhea were reported as recovered or recovering.

The final key adverse event is hyperglycemia. Adverse events of hyperglycemia reported in 46 percent of patients treated with capivasertib. This incidence is higher than the observed rate in the breast cancer population. CAPItello-281 trial enrolled more patients with type 2 diabetes., more than half had prediabetes at baseline, and the standard of care backbone is known to increase metabolic risk. Most reported events were grade 1 and 2. Grade 3 or above, defined as either insulin use or hospitalization, occurred in approximately 14 percent of capivasertib patients.

Dose interruptions and reductions, along with metformin or other oral hyperglycemic agents, were the main strategies for managing hyperglycemia. Relatively few patients discontinued treatment. Insulin was used in about 13 percent of patients with an adverse event of hyperglycemia. At the 30-day

post-discontinuation follow-up, 3.4 percent patients remained on insulin.

Lastly, the resolution rates of hyperglycemia at the end of the data cutoff were similar across the arms. So what is the impact of this hyperglycemia, and is it reversible? Here we see the hemoglobin A1C trends displayed over time. A1C on capivasertib increased by about 1 percent above baseline on average within the first few weeks of treatment and reached a mean of approximately 7 percent throughout the study. Mean A1C stays below 8 percent target, recommended by the American Diabetes Association for older patients with multiple chronic illnesses, including cancer. On the right, we see that this effect is reversible. After patients discontinued capivasertib, the A1C levels returned to baseline.

We updated our management guidelines for hyperglycemia based on our learnings from this trial along with our breast cancer postmarketing experience. These learnings are also reflected in our commitment to patient safety. Our plan builds upon a comprehensive pharmacovigilance program by

postmarketing surveillance and signal section activities from numerous sources. We will closely work with the FDA to ensure appropriate risk communication via product labeling and in the patient information leaflet, noting differences between the breast cancer and prostate cancer populations.

Finally, we will provide educational materials for healthcare professionals to support their clinical decision making. And for patients, we will provide symptom trackers to help them report any concerns to their healthcare team. This comprehensive approach supports our commitment to minimize risk in this metastatic hormone-sensitive prostate cancer population.

Now, let's shift to the impact of adverse events on patient-reported outcomes. Generally, patients reported little to no bother. In the CAPItello-281 trial, we used the Functional Assessment of Cancer Therapy-Prostate, or FACT-P, survey to collect patient-reported data on the quality of life. The FACT-P question GP5 asks patients about their overall treatment side effects.

As shown in the purple and blue, throughout the study, on average, three-quarters of patients receiving capivasertib were not bothered at all or were only a little bit bothered. We see that the high side effect bother, shown here in the orange and red, was reported by fewer than 10 percent of patients throughout the trial. Overall, despite the higher rates of any adverse event, most patients perceive low side effect bother.

So how does this translate to patients' quality of life? Here we see the FACT-P functional well-being, which captures aspects such as the ability to work, sleep, and enjoy life. Higher scores indicate better function. There are numerical differences between the arms, favoring placebo, which are not considered clinically meaningful, and scores are generally stable over time. Overall, patients are willing to tolerate manageable side effects when functional well-being is maintained.

Finally, we'll look at data from the recent safety update. With an additional 9 months of follow-up, the safety profile has remained stable

with no new safety signals. Notably, there were 77 new all-cause deaths in this update, of which 50 were in the placebo arm. The imbalance in deaths previously observed has narrowed. Overall, there is no evidence of cumulative toxicities.

In conclusion, safety profile of capivasertib is well established since its approval in breast cancer. The key adverse events of diarrhea, rash, and hyperglycemia observed are on-target effects of AKT inhibition. Patients did report experiencing side effects of treatment but did not meaningfully impact how they function day-to-day. Finally, adverse events were managed using labeled strategies requiring monitoring, dose modification, prompt intervention and, importantly, did not impact patients' ability to receive abiraterone. It is important to consider these risks in the context of the lack of targeted therapies in the PTEN-deficient population.

Thank you. And now I'd like to invite Dr. George to the podium to provide his clinical perspective.

Applicant Presentation - Daniel George

DR. GEORGE: Hello, and thank you, Dr. Patel.

I'm Dr. Dan George. I'm a Genitourinary Medical Oncologist at Duke, and as a clinician and clinical researcher, I've treated prostate cancer patients for over 27 years. As a member of the steering committee, I was involved in the design and implementation of CAPItello-281. I'm here to provide a clinical perspective on the data that you've heard. I'm a paid consultant to the sponsor, but I have no financial interest in the outcome of this meeting.

CAPItello-281 has confirmed that PTEN-deficient metastatic HSPC is associated with poor prognosis. For example, the LATITUDE study evaluated patients with de novo, high-risk metastatic HSPC, but no other biologic selection. In this trial, abiraterone and ADT demonstrated a median progression-free survival of 33 months. The CAPItello-281 study evaluated patients with high- and low-risk metastatic HSPC, but selected for at least 90 percent PTEN deficiency. In this trial, abiraterone and ADT demonstrated a median rPFS of

only 25.7 months.

Fortunately, patients with PTEN-deficient tumors can be easily and reliably identified as part of their initial assessment. Testing for PTEN deficiency is best done by immunohistochemistry, which is a standard pathologic test. It's fast, it's scalable, it's inexpensive, and it can be implemented widely. Twenty-five percent of patients have PTEN-deficient metastatic HSPC. Therefore, every patient presenting with advanced prostate cancer should be tested for PTEN status via immunohistochemistry as a standard of care, because now we have an effective treatment for these patients. Our first goal for these patients is to delay progression while maintaining quality of life, and capivasertib does this.

CAPItello-281 was a positive study that met its primary endpoint with a clinically meaningful 7.5-month improvement in rPFS. But what does delayed time to progression really mean for patients? I would tell my patient that your particular type of prostate cancer makes it more likely that you'll

experience a fracture or painful growth in your bones that could be disabling, could require surgery or radiation, and may have a lasting effect on your quality of life. Adding capivasertib can decrease these complications. Likewise, your type of cancer is likely to progress on hormonal therapy more rapidly, even without a rise in PSA, but adding capivasertib can prolong the time until hormonal therapy stops working and delay the need for chemotherapy. This matters because chemotherapy in the metastatic castration-resistant setting is life-altering with high rates of fatigue, nausea, neuropathies, serious infections, and treatment failure.

I would also tell my patient that we need to watch for signs of rash and diarrhea within the first 2 weeks. I would give them a management plan to intervene with supportive medications like topical steroids or loperamide, and I would proactively contact those patients or have them seen in clinic at that time point.

I would also counsel my patient on

hyperglycemia and frequently monitor for high blood glucose levels. We expect that most patients who receive capivasertib will experience a modest increase in hemoglobin A1C. We also know that this can be controlled with metformin. And while I would tell my patient that dose holds, and modifications, and even discontinuation may be necessary for acute or severe side effects, we know that most patients can stay on treatment and maintain their quality of life.

Based on the body of data, the benefits of adding capivasertib to abiraterone and prednisone outweigh the risks for the population with PTEN-deficient metastatic HSPC. Capivasertib is the first targeted therapy to delay progression and alter the clinical course for these patients. Other systemic treatments such as docetaxel will remain an alternative, particularly for our high-risk, high-volume patients, but many of our patients are either not fit for chemotherapy or refuse it. In addition, 36 percent of CAPItello-281 patients have low-risk cancer for whom chemotherapy is not

indicated. Capivasertib addresses an unmet need in 25 percent of metastatic HSPC patients. For these patients, the risk tolerance for adding targeted therapy with capivasertib will be an individual decision.

Now, I disagree, respectively, with the FDA that the benefits of capivasertib are too small to be considered clinically meaningful. For many patients, a median time to progression of two years is just not long enough, especially since for most patients in metastatic HSPC, their first remission is their best remission. Extending the time to progression by 7.5 months, on average, will be worth the risk of side effects that are recognizable, reversible, and treatable. Capivasertib might not be the right treatment for all PTEN-deficient patients, but all PTEN-deficient patients deserve the chance to decide, with their oncologist, whether it's right for them.

Now, as you heard from Dr. Heath earlier, our evolving understanding of biomarkers in prostate cancer is allowing us to improve patient care. Until now, we may have tested patients with metastatic HSPC

for PTEN deficiency as a prognostic factor, but it has not affected our treatment decisions because we've had no way to target it. Now that we have an effective targeted therapy for metastatic HSPC patients with PTEN deficiency, we must incorporate this precision approach. The combination of capivasertib with abiraterone and ADT should be the first choice considered for these patients. Thank you.

DR. VASAN: Thank you, AstraZeneca.

We will now proceed with FDA's presentations by Dr. Daniel Lee.

FDA Presentation - Daniel Lee

DR. LEE: Good afternoon. My name is Daniel Lee, and I'm the clinical reviewer for this application. Here are the FDA review team members, and this presentation reflects our collective input.

The FDA's discussion for today's ODAC meeting will focus on the overall benefit-risk demonstrated by CAPItello-281. We ask the committee to vote on this question. Based on the CAPItello-281 results, does the benefit of adding capivasertib to

abiraterone and prednisone outweigh the risk for the proposed indication?

In our presentation, we will explain why we brought this application to ODAC. We will discuss the magnitude of improvement in rPFS, the lack of supportive data from the secondary endpoints and from other prostate cancer studies, and the increased toxicity from the addition of capivasertib.

First, while CAPItello-281 met its primary endpoint of rPFS, we are concerned that the demonstrated magnitude of rPFS treatment effects may not be clinically meaningful. The enrolled patients had de novo PTEN-deficient mHSPC, where PTEN loss was defined by immunohistochemistry as at least 90 percent of tumor cells with no cytoplasmic staining.

Patients were stratified based on two factors. The first, a combination of volume of disease and presence of visceral metastases, and the second, geographic region. They were randomized 1 to 1 to capivasertib and abiraterone, or placebo and abiraterone, with the primary endpoint of rPFS

per investigator. Approved dosages were administered for all drugs. The key secondary endpoints included OS.

Here is the relevant regulatory history. In 2020, we stated that for a favorable benefit-risk profile, the trial should demonstrate a large magnitude of improvement in rPFS supported by OS. In the absence of a large improvement in rPFS, an improvement in OS or other clinically meaningful endpoints may be needed to demonstrate clinical benefit. We recommended including OS as a primary endpoint.

On November 2023, capivasertib was approved in combination with fulvestrant for advanced breast cancer with PI3-kinase, AKT1, or PTEN alteration. On January 2025, at a formal meeting, we advised against submission of a supplemental new drug application because of concerns around the rPFS magnitude of improvement and overall benefit-risk assessment.

The primary endpoint of rPFS by investigator was met with a hazard ratio of 0.81 and an estimated median rPFS of 26 months in the placebo arm and

33 months in the capivasertib arm. We note that the median estimates alone do not adequately characterize the treatment effect of rPFS over time. In this case, the median estimates occur in the Kaplan-Meier curves, where there appears to be a larger difference between treatment arms, but where there are fewer patients at risk.

To further characterize the treatment effect of rPFS, we also considered exploratory landmark analyses based on the Kaplan-Meier estimated proportions of patients who are progression free and alive, at every 6 months up to 24 months, as shown in the red box and depicted with vertical lines on the figure. We see that the difference between arms was only 2 to 3 percent at 6 and 12 months and only 4.7 percent at 24 months.

In general, we interpret landmark analyses cautiously, as they're based on specific timepoints rather than representing the entire rPFS distribution over time. Overall, the Kaplan-Meier curves and hazard ratio provide a more comprehensive summary of rPFS results, suggesting a modest treatment effect.

We examined the robustness of the primary rPFS findings through multiple sensitivity and supplementary analyses, which revealed important insights about the consistency and magnitude of the treatment effect. Recall our primary rPFS analysis showed a difference in median of 7.5 months with a hazard ratio of 0.81. The hazard ratio point estimates ranged from 0.77 to 0.89 across the sensitivity analyses. Although the sensitivity analyses appeared to be generally consistent with the primary analysis results, we remain concerned about the clinical meaningfulness of the magnitude of improvement of rPFS.

To assess the clinical meaningfulness of the CAPItello-281 results, we refer to the previously approved therapies in mHSPC. As Dr. Chang noted, there is concern with clinical meaningfulness of the CAPItello-281 results in the context of previous approvals in mHSPC. We will first focus on the approvals that included rPFS as a primary endpoint.

The four rPFS-based approvals were supported by trials demonstrating large clinically meaningful

treatment effects. Three of them were based on androgen receptor pathway inhibitor doublets with androgen deprivation therapy, or ADT, compared to placebo with ADT. The most recent approval was based on AMPLITUDE for the combination of niraparib with abiraterone, prednisone, and ADT in patients with BRCA2 mutated mHSPC. The control arm therapy in this trial was the same as the control arm therapy in CAPItello-281, which comprises abiraterone, prednisone, and ADT. The rPFS hazard ratio estimate of 0.46 was similar to other approvals in all-comers indications. While overall survival data were immature at the time of approval, 22 percent of patients had died on the niraparib arm compared to 34 percent on the placebo arm.

While the FDA does not have a comparative efficacy standard, this table provides examples of rPFS treatment effects that we have considered clinically meaningful. Two approvals that FDA granted for mHSPC were based on OS in LATITUDE and ARASENS trials, which led to the approvals of abiraterone and darolutamide with docetaxel,

respectively. ARASENS was a contemporary trial with an active control arm therapy of docetaxel with ADT. Regardless of whether OS is a primary endpoint or statistically significant, the FDA considers OS an important component of the benefit-risk assessment framework.

The past six approvals for mHSPC were supported by large improvements in rPFS, OS benefit, or both. In contrast, capivasertib shows a modest rPFS hazard ratio of 0.81 without OS benefit. Therefore, we question whether the rPFS improvement observed with capivasertib is clinically meaningful.

While the choice of control arm therapy in CAPItello-281 was acceptable at the time of the trial design, and this therapy remains an option, it currently does not appear to reflect the most active or preferred therapy for the enrolled population. CAPItello-281 enrolled patients with metastatic disease at initial diagnosis, and approximately three-quarters of enrolled patients had high-volume disease, defined as either visceral metastases or at least four bone metastases with at least one beyond

the vertebral bodies and pelvis.

High-volume prostate cancer that is metastatic at initial diagnosis, also referred to as de novo, or synchronous high-volume mHSPC, is associated with aggressive biology and a poor prognosis. Thus, for patients who have synchronous high-volume mHSPC and are fit for chemotherapy, guidelines and expert consensus encourage triplet therapy, consisting of an androgen receptor pathway inhibitor, chemotherapy with docetaxel, and ADT. Therefore, if the control arm patients in CAPItello-281 had received the triplet therapy, it is plausible that the rPFS benefit with capivasertib may have been even more modest.

In the absence of an improvement in OS, and with the added toxicity of capivasertib, the activity of the control arm compared to other available therapies needs to be considered to interpret the meaningfulness of the rPFS improvement. While we consider rPFS to be an acceptable primary endpoint for mHSPC, we also consider other supportive data such as secondary endpoints in our benefit-risk

assessment.

The key secondary endpoint of overall survival was not statistically significant at the interim analysis, with 51 percent information fraction. The results do not show evidence of detriment, with a hazard ratio of 0.9. An OS benefit would have addressed our concerns about the clinical meaningfulness of the rPFS results. However, given that the study design did not include a formal power calculation for OS, CAPItello-281 may not show a statistically significant improvement in OS. The final OS analysis is predicted to occur between 2027 and 2028.

Since OS was not statistically significant, all other key secondary endpoints included in the testing hierarchy were not formally tested, and their results were considered exploratory. Time to first subsequent therapy showed a hazard ratio of 0.91. The most common subsequent therapy was chemotherapy, and we note that the applicant reported results of time to first subsequent chemotherapy. Overall, both time to first subsequent therapy and time to first

subsequent chemotherapy are difficult to interpret because timing of next therapy may be dependent on factors other than progression.

For symptomatic skeletal event-free survival, results showed a hazard ratio of 0.82, and for time to pain progression, results showed a hazard ratio of 1.14. Although results for symptomatic skeletal event- free survival appeared to numerically favor the capivasertib arm, we question the clinical meaningfulness of this result, given that time to pain progression showed few events and no numerical trend for an improvement with capivasertib.

The applicant also presented other exploratory endpoints in the briefing book. The clinical relevance of time to PSA progression and time to castration resistance may be limited. The time to castration-resistance endpoint is driven by rPFS events and PSA progression events. PSA progression does not always necessitate more aggressive therapy or a biologic inflection point, as radiographic progression events are considered more meaningful. Therefore, the time to PSA progression

and time to castration resistance endpoints may provide little useful information for regulatory purposes. Overall, the results of secondary and exploratory endpoints do not overcome the concerns with the uncertain clinical meaningfulness of the rPFS results.

Capivasertib has not demonstrated additional benefit when added to standard of care therapies in other prostate cancer settings. CAPItello-280 randomized patients with mCRPC who had received prior AR pathway inhibitor but were chemotherapy naive, to docetaxel and ADT, with or without capivasertib. In contrast to CAPItello-281, patients in CAPItello-280 were unselected for PTEN status due to the rationale that docetaxel activates the AKT pathway. The dual primary endpoints were OS and rPFS.

The trial was deemed futile for efficacy, as the rPFS hazard ratio was 0.98 and the OS hazard ratio was 1.22. In addition, the prespecified exploratory analysis did not suggest a more favorable OS for rPFS treatment effects for the PTEN-deficient patients. The trial was terminated in April 2025

following IDMC recommendation for futility and safety concerns. Despite the differences between CAPItello-280 and CAPItello-281, the demonstration of futility in CAPItello-280 increases our concern regarding the efficacy and safety of capivasertib in patients with metastatic prostate cancer.

In the briefing document, the applicant stated that the potentially added efficacy from AKT pathway inhibition was supported by the phase 2 ASTON MARTIN trial. This was a hypothesis-generating trial evaluating the combination of ipatasertib, another AKT inhibitor, with abiraterone and prednisone. PTEN loss was not a stratification factor, and preliminary efficacy results should therefore be interpreted with caution, as baseline covariates might have been imbalanced.

Importantly, this trial led to a larger randomized trial, IPATential150, with 1101 patients, which evaluated the combination of ipatasertib plus abiraterone versus placebo plus abiraterone, as first-line therapy in patients with PTEN-deficient mCRPC. The trial met the dual primary endpoint of

rPFS in the PTEN-deficient population, with a hazard ratio of 0.77 and an improvement in median rPFS of approximately 2 months, but there was no improvement in OS, with a hazard ratio of 0.94.

While the rPFS result was statistically significant, FDA would not have considered this efficacy result to be clinically meaningful. While ipatasertib is a different drug from capivasertib, the trial was conducted in patients with mCRPC rather than mHSPC, and there were differences in the definition of PTEN deficiency. These results do not appear to support inhibition of the AKT pathway in patients with PTEN-deficient prostate cancer.

We have thus far discussed our uncertainty about the clinical meaningfulness of the efficacy of capivasertib when added to abiraterone and prednisone. We found a lack of data from secondary endpoints and other trials suggest a clinically meaningful effect.

Let's turn to our safety analysis to examine the toxicity profile of this combination therapy. Our summary of safety data will rely on the day 120

update to more closely reflect the anticipated clinical experience, including prolonged exposure. These data include approximately nine additional months of follow-up compared to the data summarized with a primary rPFS analysis.

Overall, the combination of capivasertib with abiraterone resulted in increased toxicity and decreased tolerability compared to placebo with abiraterone. For example, there was a 26 percent higher incidence of grade 3 or higher adverse reaction among patients treated with capivasertib compared to placebo. Eight percent of patients treated with capivasertib died due to adverse reactions compared to 6 percent treated with placebo. Twenty percent of patients treated with capivasertib discontinued capivasertib due to adverse reactions compared to 6 percent treated with placebo discontinued placebo due to adverse reactions. Ten percent of patients treated with capivasertib discontinued abiraterone due to adverse reactions compared to 6 percent treated with placebo.

While the applicant states that many of the

adverse reactions associated with capivasertib were successfully managed and reversible with supportive treatments or dose modification, the proportion of patients with fatal adverse reactions was still increased in patients receiving capivasertib compared to placebo. Among the fatal adverse reactions on the capivasertib arm, more than a third occurred within the first 3 months. This was more than double the number of adverse reactions leading to death in the placebo arm during the same timeframe.

As the median overall survival is on the order of several years for mHSPC, this imbalance of adverse reactions leading to death is alarming, especially because prior to therapy, the patients in CAPItello-281 met extensive eligibility criteria to ensure safety of trial participation. In the briefing book, the applicant states that adverse reactions leading to death were distributed over several preferred terms, and most were not assessed as causally related to capivasertib. However, the most common causes of fatal adverse reactions were sepsis, ischemic cardiovascular events, and

hemorrhage.

We observed an increased incidence of high grade but nonfatal versions of these reactions as well, highlighting that the addition of capivasertib might have increased the risk of these events. Additionally, the risk of infections and ischemic cardiovascular events may be increased with hyperglycemia, a known risk of capivasertib treatment. Therefore, capivasertib might have increased the risk of death for some of these patients.

To illustrate the potential impact of therapy on patient experience, we highlight narratives from two patients who died after receipt of capivasertib with abiraterone and prednisone.

A 74-year-old man with no history of diabetes mellitus developed septic shock with severe hyperglycemia and multiorgan failure after 10 days of therapy, dying on day 11 despite intensive care, including dialysis and vasopressors. The patient presented with severe metabolic derangement, including glucose of over 1,000, acute renal failure,

and sepsis from urinary tract infection. A 77-year-old man with no relevant medical history developed drug eruption with widespread rash, glucose of 789, and fever after 10 days of therapy, progressing to sepsis with respiratory failure, and dying on day 23 despite intensive care.

While early treatment-related deaths are not unprecedented in large metastatic prostate cancer trials, these cases highlight the need to carefully consider the benefits and risks of the addition of capivasertib to abiraterone and prednisone.

Here, we highlight some common reasons for discontinuations of capivasertib or placebo. 133 patients discontinued capivasertib, 93 due to adverse reactions and 40 due to patient decision. In contrast, 40 patients discontinued placebo, 24 due to adverse reactions and 16 due to patient decision. This observed imbalance of discontinuation between the two arms raises concern about drug toxicity and tolerability, and shows that the benefit-risk of adding capivasertib may be unfavorable, which we will discuss in the next few slides.

The most common adverse reactions with greater than 10 percent difference between the arms included infections, skin reactions, diarrhea, hyperglycemia, and anemia. Skin reactions, diarrhea, and hyperglycemia are on-target effects from AKT pathway inhibition. The incidence of skin reactions was 53 percent among patients treated with capivasertib compared to 17 percent among patients treated with placebo. Three percent of patients had erythema multiforme, most of which were grade 3.

Similarly, the incidence of diarrhea was 53 percent among patients treated with capivasertib compared to 9 percent among patients treated with placebo. These adverse reactions caused frequent dose reductions, interruptions, and discontinuations. The high incidence of hyperglycemia is also clinically relevant. We will discuss this in detail later.

While any grade adverse reactions are clinically meaningful and can impact patient experience, higher grade adverse reactions generally have even greater clinical meaningfulness, which we

will discuss next.

The most common grade 3 to 4 adverse reactions with greater than 5 percent difference between the arms included infections, skin reactions, hyperglycemia, and diarrhea. Common infections included urinary tract infection and pneumonia. The criteria for grade 3 or higher skin reactions are limitation of self-care activities of daily living, or covering greater than 30 percent of body surface area. Such skin reactions occurred in 17 percent of the capivasertib arm compared to less than 1 percent of the placebo arm.

Overall, CAPItello-281 demonstrated an increased incidence across almost 40 terms related to skin reactions. These included terms that are not typically considered rash, such as dry skin, skin fissures, and pruritus. Thus, our analyses captured higher numbers compared to the applicant's analyses, limited to fewer terms. Overall, grade 3 to 4 adverse reactions, including many life-altering events, occurred in 63 percent of the patients treated with capivasertib. Although the applicant

states that many of these are managed and reversible with supportive treatments or dose modification, supportive treatments still increase patient burden. We will examine this further in the next slide focusing on hyperglycemia.

Hyperglycemia was a common adverse reaction with greater overall and grade 3 to 4 incidence in the capivasertib arm compared to placebo. Among the 15 percent of patients in the capivasertib arm with grade 3 to 4 hyperglycemia, 6 patients, or 1.2 percent, had diabetic ketoacidosis or DKA. There was also a death due to DKA. The median time to onset of DKA was almost 9 months, highlighting the risk of serious toxicities with cumulative and prolonged exposure to capivasertib.

In CAPItello-281, 17 percent of patients required initiation with insulin. The rates of grade 3 to 4 hyperglycemia, and initiation or change of antihyperglycemic medications such as insulin, were several-fold higher in this trial compared to the breast cancer trial that led to approval of the drug. This likely reflects the risk of combining

prednisone with capivasertib in CAPItello-281.

Additionally, exposure to capivasertib was longer. The median drug exposure was 17 months in CAPItello-281 compared to 5 months in the breast cancer trial. Thus, while the applicant considers the safety profile to be consistent with the known safety of capivasertib, there are unique challenges for patients with prostate cancer.

Patient-reported outcomes help gain a complete picture of tolerability. PRO-CTCAE and FACT item GP5 were among the PRO measures used to assess patient symptoms and functioning in CAPItello-281. As we observed with the clinician-reported adverse reaction data, patients in the capivasertib arm consistently reported a higher rate of diarrhea and severity of skin symptoms while on treatment. For example, at week 8, half the number of patients who received capivasertib compared to placebo, 38 percent versus 75 percent, reported freedom from diarrhea in the preceding 7 days.

Overall side effect bother can be used as a measure when patients may experience a wide range of

potential treatment-related side effects that impact day-to-day functioning, such as diarrhea or skin toxicity. The FACT item GP5 is a summary measure of the overall impact of treatment toxicity. Patients indicate their response to, I am bothered by side effects of treatments, and in CAPItello-281, patients in the capivasertib arm had higher rates of bother after baseline.

In the stacked bar charts, the light blue bar indicates no bother and the other colors indicate increasing levels of bother up to very much. Note the greater percentages of patients who reported somewhat, quite a bit, and very much bother in the capivasertib arm compared to the placebo arm. For example, at the first post-baseline assessment timepoint on week 4, the majority of patients in the capivasertib arm reported some level of bother, including 10 percent with severe bother defined as quite a bit or very much. Similar results were observed through week 52.

Additionally, while the proportion of patients reporting very much bother appears to

decrease after week 4, many of the later timepoints do not include patients who discontinued treatment due to adverse reactions. Overall, the patient-reported outcomes strongly support the clinician-reported adverse reactions and clearly show that patients who received capivasertib had higher rates and severity of diarrhea and skin symptoms, which impacted the overall side effect bother.

Overall, the combination of capivasertib, abiraterone, and prednisone led to high rates of toxicities such as hyperglycemia and rash, accompanied by complications. Patient-reported outcomes results are in line with the observed clinician-reported adverse reactions and treatment discontinuation results, demonstrating that there are tolerability concerns with capivasertib.

Although many of the common adverse reactions observed with capivasertib are known on-target toxicities associated with the AKT pathway, the proposed indication in mHSPC presents a higher risk of hyperglycemia in combination with prednisone compared to the approved indication in breast cancer.

Additionally, the higher proportion of patients with drug discontinuation before progression of disease in the capivasertib arm raises concern that the efficacy results may not be clinically meaningful.

The applicant states that the adverse reactions with capivasertib in combination with abiraterone are of similar incidence and nature to those observed with other intensification regimens in mHSPC. However, much of the high-grade toxicity reported with triplet regimens containing chemotherapy were hematologic, which are qualitatively distinct, particularly in the context of its shorter duration of therapy.

I will now summarize our assessment and concerns related to the proposed application for the treatment of patients with PTEN-deficient mHSPC. CAPItello-281 demonstrated a statistically significant improvement in rPFS. However, we are concerned that the benefit-risk of adding capivasertib may be unfavorable in the absence of OS benefit. Furthermore, the addition of capivasertib to abiraterone and prednisone was accompanied by

increased toxicity, including higher rates of grade 3 or higher adverse reactions, including deaths, need for antihyperglycemic medications, and insulin.

We request the committee to consider the clinical meaningfulness of these findings. The relevance of delaying progression must be weighed against the toxicity burden in an early metastatic population with few baseline symptoms. Patients and providers cannot distinguish capivasertib efficacy from abiraterone for individual patients. Because capivasertib is added to an effective therapy, even patients not benefiting may be exposed to it for extended periods.

While PTEN deficiency appears to be a poor prognostic marker, the control arm outcomes reflect the degree of unmet need. In the control arm, the majority of patients had few or no symptoms, median rPFS was more than two years, and median OS is not yet reached. Ultimately, in both a biomarker-selected population or an all-comers population, for an add-on trial design, the magnitude of the treatment effect needs to be considered in the

context of the added toxicity.

The discussion topic and question for the advisory committee is, based on the CAPItello-281 results and safety data, does the benefit of adding capivasertib to abiraterone and prednisone outweigh the risk for the proposed indication?

This concludes my presentation. Thank you for your time.

DR. VASAN: Thank you.

We will take a quick 10-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume at 3:30 p.m.

(Whereupon, at 3:19 p.m., a recess was taken, and meeting resumed at 3:30 p.m.)

Clarifying Questions

DR. VASAN: We will now take clarifying questions to the presenters. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter if you can. If you wish for a

specific slide to be displayed, please let us know the slide number if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member. So if people could just put up their placards, and we will take note.

I will start for the first clarifying question to the sponsor. Neil Vasan, NYU Langone. You showed PFS by bins for PTEN. Do you have those data for overall survival?

DR. FOXLEY: We don't have those in the deck. No, I don't believe so.

DR. VASAN: SO there's no analysis of --

DR. FOXLEY: I'll ask Chris Gresty, our statistician, to come to the podium.

DR. VASAN: Okay.

DR. FOXLEY: We don't have them. Sorry.

DR. VASAN: All right. And the second question --

DR. FOXLEY: May I just follow up with that?

DR. VASAN: Yes.

DR. FOXLEY: The reason for that is that we were at 26 percent maturity at the time of the primary analysis, so cutting into bins for overall survival would have been very unreliable. So we didn't do that for OS.

DR. VASAN: All right.

DR. SUZMAN: Sorry. I believe we have those available. If you'd like to put up --

DR. VASAN: Oh, okay.

DR. SUZMAN: -- backup slide 54.

DR. CHANG: Backup slide 54, yes.

DR. VASAN: Sorry. Can you please introduce yourself?

DR. SUZMAN: Yes. Sorry. Daniel Suzman, FDA. Please put up backup slide 54 from the FDA deck.

(Pause.)

DR. VASAN: I don't know if the FDA wants to describe what's on the slide, commentary.

DR. CHANG: I can start. This is Elaine Chang, FDA, clinical, and then our statistical colleagues can chime in. We have the different

categories. PTEN loss greater than equal to 90 is the ITT, and then PTEN loss greater than equal to 95 percent loss, and then 100 percent loss.

So you were interested in the OS analyses, and in the red box, you can see the patients that have more loss, and then in the green box is the complementary subgroup. So patients who have less, like between 90 to 95 percent, the OS hazard ratio was 1.72 with a 95 percent conference interval of 0.93 to 3.3.

So we acknowledge that there appears to be some trend, and some of these small groups may not be that small. You can see the n's in the rPFS column, 814, 198, but these subgroups are still exploratory. PTEN loss was not a stratification factor. The range, I think since the OS results -- even an ITT population was not significant, so I think we would focus more on the rPFS results. And even the rPFS results, for example, 0.7 to 0.77, those effects were not in the range of what we have considered clinically meaningful in the past, the other FDA approvals.

The other point that I would make is that the diagnostic, the IVD, the in vitro diagnostic, was validated at the 90 percent level, so considering, these other cutoffs would require additional validation work.

DR. VASAN: Thank you. That is all.

The next question is Dr. Rini.

DR. RINI: Thanks. I appreciate it. First of all, I want to congratulate the sponsor for a great presentation and also congratulate you for doing a prospective biomarker-based trial. We talk a lot about doing it, but very few sponsors have the guts to pull it off, so I congratulate you on doing it.

I think we've heard a lot today about benefit-risk and concerns from the FDA. So my question, maybe to one of the clinicians in the room, Dr. Heath or George, is by my back-of-the-envelope calculations, it seems the number needed to treat to prevent an rPFS event is about 15. But about 17 percent, or 1 in 6, required insulin, which I found quite a high number and quite a disturbing toxicity.

So help me reconcile that, or how would you reconcile that sitting in front of a patient if you're presenting them this option?

DR. FOXLEY: Dr. George?

DR. GEORGE: Yes. Dan George, Duke. Yes. So they're really important points, but they're very different. So when I think about rPFS, it's kind of how you define in a number needed to treat what is an rPFS event. So in these cases, we're talking about symptomatic skeletal event, we're talking about a death, or we're talking about a radiographic progression. So these are significant life-altering events for these patients.

When you talk about the need for insulin, the need for insulin was relatively low, but it was also relatively short. The median time on insulin was 8 days. These are essentially patients that show up with a high glucose. We have to hold drug. We have to get them on insulin. A week later, they're back down, and they're off drug, and we've had metformin on board. So it's a very transient short period for most patients.

The number of patients that end up long term, I think it was like 3.4 percent. So this is a much, much lower long-term concern than, say, the progression, the radiographic progression event. So to me, when we're talking to these patients, and we're recognizing that for this disease, we don't have any other proven prospective drug that can change this outcome, being able to do that is really key, and recognizing that, yes, we have to recognize this risk. We have to be on top of it. But it's a manageable risk long term in most of those patients.

DR. RINI: Thank you.

DR. VASAN: Thank you.

The next question is Mr. Conway.

MR. CONWAY: Thank you, Chair. I direct this question I guess to Mr. Foxley or to Mayur Patel, and it's this. Thank you very much for your presentation. I found it very informative, as well as the FDA's. There's been a lot said today about patient burden, some aspects of quality of life and patient-reported outcomes. As a kidney patient and also as a prostate cancer survivor, I find that

interesting when it's talked about.

Could you step out of your PowerPoint and tell us how you used patient insight data and lived experiences to inform the work that you did on this study and the trial? You've been clear about it on several slides, but what is it about this population that informed your work throughout the study?

DR. FOXLEY: So in terms of direct contact with patients, we did not do that during the course of the study. We did, however, talk a great deal to our steering committee, who have first-hand experience of managing those patients and the toxicities they'd face.

I'd like to ask Dr. Heath to come to the podium because she manages these patients on a day-to-day basis and can give you some insight into how they think about their disease and how they think about that balance between benefit and the burden that they may face from the therapies.

DR. HEATH: Thank you so much for your question. It's just so relevant for us in practice and recognizing what patients have to go through.

The diagnosis itself, obviously, of metastatic disease is devastating in any way, shape, or form, but how to really get to the treatment plan, what is the next step, is everything. And patients, as you've said, go through a lot, stay on different drugs, and have to endure a lot. But if we know that the treatment offered is their best first step, there is some comfort to that.

To your point, what do patients have to undergo? Stepping out of all of the charts and the figures, what does this really mean for a patient I would see in my own practice come Monday morning at Mayo Clinic, it would mean that I would have a very careful shared decision making discussion.

What I've learned, what we've all learned, not just from this prostate study but also from our breast cancer colleagues, is the side effects are real but manageable. Early intervention, as noted by the package insert, because it is an approved drug, tells you exactly what to do. I think these are things that when you're in the thick of a trial, you don't always know. You're doing things as prescribed

from years of implementation, and then you execute. And then at the end you say, boy, had I known, and so on. But what I feel is important for patients, and what I would offer, is what I believe is the right treatment for this really aggressive biology cancer.

I'll tell you a frightening thing that I found during this process, too. When you see a patient that progresses on their scans, and it catches you off guard because those metastatic hormone-sensitive patients, they don't get routine scans -- this is not the mCRPC space where they're just showing up every three months doing things. So here, you're relying on PSA a lot. And when you don't see that worsening, but then get caught from the scans progressing, you start to realize, this is a different biology. So early intervention, education, awareness, I think is really the key to success here. Thank you.

MR. CONWAY: Thank you.

DR. VASAN: Would the FDA like to comment? I think this is a very important point about toxicity and what this would look like in the real world.

DR. BHATNAGAR: Absolutely. Vishal Bhatnagar, FDA. So I think tolerability and toxicity is something that's really important to measure from the patient perspective. And to that point, it's patients that have to reconcile with the side effects of these therapies on a daily basis. One of those side effects, many were mentioned, is diarrhea. So I'd ask if we could pull up backup slide regarding PRO-CTCAE data on diarrhea.

DR. SUZMAN: Daniel Suzman, FDA. That's backup slide 73.

DR. BHATNAGAR: Thank you. So as you can see, although the applicant says that this is well managed, what we see in the PRO-CTCAE question about the frequency of diarrhea is that there's a group of patients that have almost constant diarrhea. And when you ask patients how they're doing, a frequent or almost constant amount of diarrhea is obviously problematic. There's obviously an imbalance here.

But to your point in terms of stepping out of the bar chart, it's this idea of overall side effect bother and almost constant symptoms that patients

have to reconcile with on an almost daily basis. And although, again, we can say that they're easily managed, the whole point of asking these questions is to get to this heart. CTCAE or clinician-reported AEs may not get to that. PROs do, and we shouldn't ignore that.

DR. FOXLEY: May I add?

DR. VASAN: Yes.

DR. FOXLEY: So we have learned from this trial, and we've learned from our experience in breast cancer. And we have with us today Dr. Hope Rugo, who has first-hand experience of managing this toxicity with patients. I think it would be useful to hear from her, how the learning over time has helped with that.

DR. VASAN: All right. Thanks.

DR. RUGO: Thank you. I'm Hope Rugo, Breast Medical Oncologist at City of Hope, and I have no financial benefits from this presentation or approval, but I am on the steering committee for CAPI-291 and 292, which are phase 3 trials for breast cancer. I have given a lot of capivasertib to breast

cancer patients, as well as other drugs that we use, as many of you are familiar with, that cause diarrhea and we're giving now in many stages of breast cancer.

And what we've learned about managing diarrhea with these drugs is that we talk about diet, not to change your diet but to use prophylaxis after you know what an individual's experience is to avoid constipation. So in that situation, what we've done in our publications and teaching is to describe the use of antipropulsive agents in a preventive manner. For example, if you're going to go on a big hike, you want to take an antipropulsive agent beforehand or if you're going to have a big salad. I mean, these sound like very straightforward recommendations. Take a half a pill if a whole pill makes you constipated. We've really learned a lot and we convey that to our patients.

So although we saw diarrhea early with capivasertib, now once we get the individual patient experience, we can prevent it. It's not cumulative over time. And I think you can see that from these bar graphs. It's what it is for an individual

patient, and by using this proactive approach, we can control the diarrhea so that even a smaller number of patients have the frequently or almost constantly effect.

DR. CHANG: Elaine Chang, FDA. I just would add that I think the breast cancer experience is valuable, but there are unique challenges with prostate cancer. We saw that the median exposure with the breast cancer trial was 5 months, and in the prostate cancer trial, it's 17 months. So there are some unique considerations for the clinical context, and the labeling, ultimately, cannot address the issue that the contribution of capivasertib, apart from abiraterone, for an individual patient will not be assessed.

DR. VASAN: Thank you.

The next question is Dr. Choueiri.

DR. CHOUEIRI: Tony Choueiri, Dana-Farber, Boston. I have a question for the sponsor, actually more than one question. I want to go to table 36. I wish it was table 6. And it was put here, the magnitude of the benefit based on PTEN loss. I would

like to see -- I hope you have that analysis ready -- the hazard ratio for PFS and OS, excluding the population that has complete loss, 100 or 99 percent loss. I want to focus on 90 to 98 alone and 99 and 100, and see the hazard ratio for both, if that can be done even during. So that's one, if it's possible.

And second, I would like you to focus more on this immunohistochemistry test for PTEN loss. These are archival specimens. Did you run an analysis if your specimen is over a year from cycle 1, day 1? What if this is a biopsy done 7-8 years ago? How does the test perform? I think this is important. Thank you.

DR. FOXLEY: Certainly. If I may, whilst we're gathering data for your question about the cutoff, I'll ask Dr. Lotan, our expert pathologist, to come to you and talk to you about the IHC issue that you raised, and we'll look for the data for the other piece.

DR. LOTAN: Tamara Lotan. I'm a GU pathologist at Johns Hopkins. I am a paid consultant

to the applicant.

DR. CHOUEIRI: Please raise your voice.

DR. LOTAN: Sorry.

DR. VASAN: I'm sorry to interrupt. Dr. Choueiri was referring to table 36 in the briefing document.

DR. CHOUEIRI: Thirty-six.

DR. LOTAN: Sorry. Tamara Lotan, GU pathologist from Johns Hopkins. I am a paid consultant to the applicant but don't have any financial interest in the outcome of this meeting. So we actually routinely do PTEN immunohistochemistry at Johns Hopkins prospectively as a prognostic biomarker, and have found that specimens going back even 10, 15 years are still highly interpretable, in general.

We have good internal controls because we have benign tissue in the sample and benign stroma so that we can determine if the samples are not a valid result if that stroma is not staining. But that generally happens in less than, I would say, 10 percent of cases. And we've done many studies

looking at the preanalytic variables like fixation, block age, age of specimens. So it works fairly well in archival specimens.

DR. CHOUEIRI: But what's the experience outside of Hopkins, like in Iowa and community oncology, where 80 percent of oncology care happens? Are they going to be able -- they're not all Hopkins trained. So how is this biomarker going to perform?

DR. LOTAN: So I think it's a very straightforward biomarker to interpret, especially in the context of this increasing menu that we're getting with ADCs, which have very complicated scoring systems. I think we're helped by two points here. One is that in the initial presentation, where they showed the distribution of percent of cells with PTEN loss, you see that it's really bimodal. You generally have cases with almost complete loss or cases with very minimal loss, so that's helpful. And I think the very simple scoring system, where we're not doing a complex H-score with intensity and so forth, makes it very easy to translate. And we have very high inter-reader reproducibility.

DR. CHOUEIRI: Even with specimen 5, 10 years old?

DR. FOXLEY: So this population was de novo, so the issue of age of sample becomes less relevant because this is part of the diagnostic workup. So the biopsies that were taken were taken for entry to the study. So I'm not quite understanding your concern about the long --

DR. CHOUEIRI: They're de novo metastatic, but they could have presented the de novo metastatic disease, but they would have had high risk before, no?

DR. FOXLEY: No, these presented de novo.

DR. CHOUEIRI: And where the biopsy was done, is there any difference between primary or metastases?

DR. FOXLEY: I'll ask Elza de Bruin, our -- sorry. Kyra Mumford, our biomarker expert, can tell you exactly what the mix of those samples was.

DR. MUMFORD: Kyra Mumford, Precision Medicine. The samples were collected as part of

standard of care priority enrollment under this study, and the vast majority, greater than 95 percent of them, were from primary tissue, and greater than 95 percent from a biopsy.

DR. FOXLEY: So turning to your other question, I think your question was actually about the grouping of outcome by an IHC score of 90 to 98. Am I correct, Dr. Choueiri?

DR. CHOUEIRI: Yes.

DR. FOXLEY: So neither the FDA table, I don't think, nor ours does that. But I would like to show you slide 4. Up, please. Here, you can see above the line -- we don't have the data for the 90 to 98, but what you do see in the upper plot, which is the capivasertib arm, is the cutpoints that we have analyzed, so 90 to 94, 95, 99, and 100. And what you see there is that the capivasertib Kaplan-Meier curves for each of those groups overlie each other, whereas in the placebo arm, working from the bottom, the 100 percent loss are at the bottom of the colored curves, and they cluster together. 95, 99, and 100 are overlaid, and somewhat anomalous is

the finding for the 90 to 94 group who appear to do incredibly well. We don't really regard that as biologically plausible. It's the smallest group, and so we have had some difficulty interpreting that result.

DR. CHOUEIRI: That doesn't answer the question.

DR. FOXLEY: I don't have a plot for you for 90 to 98.

DR. CHOUEIRI: I just want to see table 36, another analysis that has 99 and 100 together and 90 to 98. I want to see the hazard ratio for PFS and OS in both.

DR. FOXLEY: That's slide 2 up.

DR. CHANG: This is Elaine Chang, FDA. I think what you are asking about, the 90 to 98 percent, that would be in the PTEN loss greater than and equal to 99 in the "No" column, n equals 611, 60 percent of the population, the hazard ratio for rPFS was 0.94 and the OS was 1.02.

Is that what you're looking for?

DR. CHOUEIRI: Yes, but I didn't see that

analysis. You have that.

DR. CHANG: That's the FDA's analysis.

DR. CHOUEIRI: Okay. I didn't see that slide. So you're telling me if there is 90 to 98, meaning excluding the 99 and the 100, the hazard ratio for PFS is 0.94 and for OS is 1.00?

DR. CHANG: .02.

DR. CHOUEIRI: Okay. Thank you. No further questions.

DR. VASAN: Next, Dr. Huang?

DR. HUANG: Thank you. Franklin Huang, UCSF in San Francisco VA. This is a question for the sponsor. I'm curious. Given the higher burden of prostate cancer in black or African American men, I guess ideally would have seen more enrolled patients in the mHSPC setting here. And I'm curious as it relates to PTEN deficiency. We know that PTEN deficiency is less common in African American men, so I'm curious. In the screening process, do you have any data on whether more men were screened out? And also, could you comment on implications for this patient population?

DR. FOXLEY: We have looked at this. Dr. Gaia Schiavon could come to the podium and answer your question.

DR. SCHIAVON: Gaia Schiavon, Clinical Development. Yes, a very important question. Slide 1 up, please. We have certainly looked at this very carefully. We have screened 191 patients, black African American, that tested 178. I identified 22 PTEN-deficient patients and randomized 12. So this indicates slightly -- we know that, especially in the U.S., there is a high incidence of prostate cancer for this population. But this real-world evidence indicated that PTEN deficiency, the prevalence is slightly lower than in the global population. We don't expect, however, that the biology would be different. So in terms of implication, we would expect PTEN-deficient mHSPC prostate cancer in this population to be as aggressive as we have seen in CAPItello-281 overall.

DR. HUANG: Thank you, guys. One other quick question, which was, did you check in terms of other co-occurring genomic alterations that would

contribute to the heterogeneity of the rPFS, a response in different PTEN categories?

DR. FOXLEY: Those analyses are underway, but we haven't completed anything and couldn't show you anything on that today.

DR. VASAN: All right. Any other clarifying questions?

(No response.)

DR. VASAN: I want to just ask one clarifying question to the FDA. Just thinking about precedence, the one trial that I'm thinking about here is SOLAR-1, where we had -- this is apples and oranges. It's a different disease. It was a second-line setting but a PFS benefit, no OS benefit, a very toxic drug that didn't go to ODAC, that got FDA approved.

Could you just maybe try to compare -- I realize that was seven years ago -- and contrast how you see this as substantially different, the cognitive exercise that we're trying to do today?

DR. SUZMAN: Daniel Suzman, FDA. I'll let our experts in the other diseases comment on those.

I guess our question to the committee today is really around what is a clinically meaningful improvement rPFS in this specific disease context. And with the toxicities that we're seeing, with the addition of that drug for an add-on therapy, the acceptable threshold for efficacy and treatment effect, I think it's going to differ, again, between different populations, different drugs, different disease settings. And we're really curious about -- and, again, we have not approved a drug for prostate cancer, and specifically hormone-sensitive prostate cancer, with this magnitude of treatment effect as an add-on therapy. So again, I think it's a question to the committee about the clinical meaningfulness of the demonstrated results.

DR. AMIRI-KORDESTANI: I want to add that we look at hazard ratios. So the hazard ratio of this is not similar to -- in addition to everything that Dr. Suzman mentioned.

DR. VASAN: Thank you. That's all for my questions.

Dr. Rini?

DR. RINI: Thank you. Brian Rini, Vanderbilt. So one more question for the sponsor about not allowing the use of chemotherapy, given that 75 percent of your patients were high volume, and it would be a standard of care with the survival benefit. So just walk me through the decision not to allow that. And I think, thinking as a clinician, it would complicate the decision for a high-volume patient with PTEN deficiency because I have a therapy that extends survival and one that doesn't, and I'm not sure how to make that choice.

DR. FOXLEY: I will begin by just rehashing the history. At the time we started CAPItello-281, those trials of triplet therapy containing docetaxel, ADT, and ARPI had not read out. And so ADT-ARPI was the standard of care at the time. What we do know about docetaxel is there's been a step forward. The ARASENS study looked at that. But it's important to remember that ARASENS compared docetaxel in both arms and had ARPI added in one and not the other, and there's no reporting of the outcome for PTEN deficiency per se.

I think what's critical here is, given where we are with the data available here, which is positive in a PTEN-deficient population for capivasertib, how that would be weighed up in the clinic. And I'll ask Dr. George to comment how that equipoise in decision making would be handled with a patient.

DR. GEORGE: Yes. Dan George, Duke. I think that the use of docetaxel for these high-volume patients, Dr. Rini, is still going to be a reasonable choice. And that's in our guidelines, and it's still level 1 evidence there. I think what the addition of PTEN deficiency does for us, it gives us another level of data, of biology, of high-risk feature to consider. Remember, with docetaxel, we're treating for 4 and a half months, and then it stops. It's not going to preferentially wipe out this AKT biology, and that's going to presumably resume off the chemotherapy then. So there's potentially opportunities to think about how you would use these agents, either in our clinical context, either in layering, or other settings.

In addition, as you know, a number of our patients are just not fit for chemotherapy. When we do a trial where we have chemotherapy in the control arm, we select a subset of patients that are chemo fit. It's not necessarily representative of the broader population. In many respects, this study, by having a broad standard of care option, allows for a broad spectrum of patients to be involved in a study and makes it probably more clinically relevant to that real-world population.

But at the end of the day, for these patients with PTEN deficiency and aggressive disease, we need more options, not less. Four and a half months of docetaxel, I'm sorry, it's just not solving the problem for these patients. And if this is an agent that demonstrates clinical benefit and with toxicities that are known, granted, maybe not all patients are going to be able to tolerate that, but for the majority of patients who can, it is a good option for those patients. So that's what we're looking for here.

DR. RINI: Just a real quick follow-up for

Dr. George. So you're correct, of course. Many patients are chemo fit. Do you think those patients would be fit for this drug? The rates of grade 3 toxicity are about the same. Obviously, the duration of this therapy is longer. So I'm wondering if those are largely overlapping circles of unfit patients.

DR. GEORGE: They're very different toxicities, though, right? Because I think we're not talking about neuropathies or other cytopenias and what not. Yes, there are complications here, but I think now that we are aware of these complications, we can treat those complications before we even start the drug. I think one of the most important things in our clinical practice is that we don't have to jump in immediately on day 1 with every therapy. We can get a patient started on hormonal therapy. We can manage diabetes. We can manage other concerns and whatnot, and then we can start a drug. And remember, this is 4 days on and 3 days off, so there's immediate breaks built in. And these breaks actually allow for these toxicities to come down.

So that's the opportunity that we have with

real-world practice with this drug, especially an oral therapy, kind of customize it to what the patients can tolerate. So yes, I do think we have a lot more flexibility with an oral intermittent therapy than we do with an IV chemotherapy.

DR. VASAN: Thank you.

Dr. Suzman, do you want to respond?

DR. SUZMAN: Sure. Daniel Suzman, FDA. I would just add to the question of were these patients chemo fit, that 80 percent of patients on the placebo arm did receive subsequent cytotoxic chemotherapy in a later-line setting, suggesting that the majority of these patients were, in fact, fit for chemo, at least in this trial. And therefore, the toxicities that we see on this trial reflect those of a chemo fit population. Thank you.

DR. VASAN: Dr. Robinson?

DR. ROBINSON: Kyle Robinson, University of Pennsylvania, Philadelphia. For the sponsor, the patients who developed hyperglycemia or diabetes on treatment -- sorry, a 2-fold question -- for the ones who went on metformin, how did that affect their

rates of diarrhea? And for the patients who weren't on metformin, were the diabetic drugs covered by the sponsor or by the patient's insurance?

DR. FOXLEY: There are two parts to that question. Dr. Rugo can tell us about the insurance coverage, and I'll ask Mayur Patel from Patient Safety to come and talk to you about the diarrhea and metformin.

DR. PATEL: Mayur Patel, AstraZeneca. When looking at the adverse events by diabetes/non-diabetes, we saw that serious adverse events and grade 3 adverse events were similar in diabetics and non-diabetics. We didn't specifically then drill down to look at whether the diarrhea was different between patients that got metformin and those that did not. Thank you.

DR. FOXLEY: Dr. Rugo, could you come and talk about insurance coverage for diabetic drugs?

DR. RUGO: Generally, the diabetic medications are paid for by the patient's insurance, and this is true, in general. When we give growth factors for patients on study, we actually charge it

to the insurance company. It would be very hard to invoice pharma for that with chemotherapy, so we have. I will say that during the conduct of these trials, over a time period, oral hypoglycemics have changed tremendously, and our experience with managing hyperglycemia has as well. It's kind of surprising because we know the names from the jingle on the television, but our colleagues in endocrinology help us a lot, and the new oral hypoglycemics are enormously more effective.

So I haven't put a patient on insulin who had even type 2 diabetes, and now several years because of these agents being available, or maybe two years, because insurance covers the drugs. But that wasn't the case in the past.

DR. VASAN: Thank you.

Mr. Conway?

MR. CONWAY: Thank you very much. Paul Conway, American Association of Kidney Patients. Two clarifying questions to FDA. The first question is, it seems to me, based on the discussions and in the briefing documents, you've tied efficacy, in part, to

healthcare utilization. And I'm wondering if you have an objective standard for that because it seems to me it's tied to the discussion about side effects. And my question specifically is, one, how do you arrive at that? And two, do you also take into account, then, therapies that delay disease progression and what potential cost savings are in terms of lower utilization? And if not cost savings, lower utilization? That's the first question.

The second question that I have to FDA is, there's been a lot of discussion about clinical meaningfulness. Now, on the device side, FDA has pioneered the science of patient insight data. And I'm just wondering, what do you ground or baseline this discussion, in terms of patient burdens and efficacy, for patients in, on the drug side? What type of feedback have you gotten from patients in terms of lived experience and patient insight data for this specific population? Thank you.

DR. CHANG: Hi. Elaine Chang, FDA. For the first question, I'm not sure if I understand what you were referring to by healthcare utilization but, in

general, we consider efficacy and safety separately, and we don't consider the cost as part of our regulatory decision. In our presentation, we referred to healthcare utilization when we discussed the use of supportive care medications to manage the toxicities.

And then for the second question, I would like to invite Vishal Bhatnagar, Patient Outcomes Associate Director of OCE.

DR. BHATNAGAR: Very briefly, Vishal Bhatnagar. So there were some disease symptom improvement measures that were deployed in the trial. However, there was no benefit seen in terms of function or symptoms when it came to disease-specific symptoms. But that is the type of information that would point to a benefit in terms of healthcare utilization or health outcomes for patients with a type of cancer. I hope that answers your question. Just to summarize, it was collected, but no benefit was seen.

DR. VASAN: Thank you. Neil Vasan, NYU Langone. I had one more question to piggyback, of

what Dr. Choueiri had discussed a couple minutes ago. When they have these PTEN IHC cutoffs, can a clinician be confident about the difference between 95 and 98, or 98 and 99, those bins that you had? I just really wanted to drill down into that specificity because there's clearly some dose response. We have to interpret what the meaning of that is. But can a clinician in the community, when they're treating a patient, be confident, and what's the stability of this test?

DR. FOXLEY: We have looked at that. Dr. Lotan, our expert external pathologist can talk to that point.

DR. LOTAN: Tamara Lotan, Johns Hopkins. So GU pathologists, or pathologists in general, are very familiar with quantifying different Gleason patterns and so forth. In this particular test -- and I don't see the exact slide I'm looking for -- the 90 percent cutoff and 95 percent cutoff had almost identical or very similar levels of -- so slide 2 up, please -- inter-reader reproducibility. So it was fairly reproducible across both of those cutoffs.

DR. CHOUEIRI: I have a question. So a lot of these patients, in practice, may have been put on ADT, then perhaps got a biopsy or something, especially if they come with high PSA. Do we have any idea what happened with PTEN protein, immunohistochemistry, once you're exposed to ADT, for example?

DR. FOXLEY: The sponsor hasn't looked at that, but I think Dr. Lotan may be able to answer from her past experience in this area.

DR. LOTAN: Dr. Tamara Lotan, Johns Hopkins. That we have not looked at either.

DR. CHOUEIRI: Okay. Another question for you. What's the turnaround time for PTEN IHC?

DR. LOTAN: So the test can be done in 6 hours. In general, we do an overnight turnaround at Johns Hopkins.

DR. CHOUEIRI: Are you developing any AI tests to get it even faster so that centers could send you the result, and you can interpret them, rather than just doing it there?

DR. FOXLEY: We've not yet looked at AI

approaches for this. We could well do so if we have an approval.

DR. CHOUEIRI: One final. In my understanding, 99 and 100 are 30 percent of the population; correct? Included.

DR. FOXLEY: Can we bring that slide up?

DR. CHOUEIRI: Table 36.

DR. FOXLEY: Table 36.

DR. CHOUEIRI: Thirty-one. Okay.

DR. FOXLEY: Sorry. Change. Table 31. No. Slide down. So the question, team, is do we have the prevalence by those cutoffs? Table 36.

DR. CHOUEIRI: Okay. So it's 33. That's yes/no.

DR. CHANG: Elaine Chang, FDA. I think it was 33 percent with 100 percent loss, and then 40 percent with 99 percent loss.

DR. CHOUEIRI: No. No. It must be lower. That's nothing. That's yes/no. That's yes/no. What's the percentage of your accrued patient that has 99 and 100 percent loss?

DR. FOXLEY: Can we bring slide 1 up? It may

be helpful. We haven't actually calculated it in the way you're asking.

DR. CHANG: It's the yes column, Toni, I think.

DR. FOXLEY: Forty percent, micro, 99 and above accounts --

DR. CHOUEIRI: Forty percent of the population. So that's 10 percent of all metastatic castration-sensitive, first-line prostate cancer. Okay. No further questions.

DR. VASAN: Yes. Dr. Huang?

DR. HUANG: Thanks. Franklin Huang, UCSF, a question for sponsor and FDA. It occurred to me when you put up that 44 percent of patients received capi with abi required initiation or change in hyperglycemics, and 17 percent initiated insulin and 6 patients at DKA, I'm curious. To what extent do you know if that's related to the length of treatment?

And then to the FDA, as we consider clinical benefit versus risk, I'm curious to what degree of the toxicities we're evaluating here would balance

the degree of rPFS that you guys are considering here, given the known side effects in question, of the known side effects of the drug?

DR. FOXLEY: Who would you like to go first? Sponsor?

DR. HUANG: Sure.

DR. FOXLEY: So we have data on that, and Dr. Patel can talk to it. We initiated increased guidance for hypoglycemic monitoring during the lifetime of the trial, and that may also have had some impact on the rate of events.

DR. PATEL: Mayur Patel, AstraZeneca. The hyperglycemia that we observed in the trial, FDA provided the median time to onset. Actually, the diabetic ketoacidosis cases had a range of dates. And so when we look at these patients very carefully, the thing that we noticed most is poor glycemic control being a critical risk factor, in addition to patients themselves had precipitating factors.

So from the patient that FDA quoted that died, we have been really looking at our toxicity management, adverse event management guidelines,

throughout the clinical trial, and we have increased the frequency of glucose monitoring. We've, in addition, educated the clinicians to further look at A1C because that will show every 3 months how that glycemic control is being maintained. Also, because there's urinalysis in these patients, really pay attention to the ketones. All of these were steps that we took to make sure that clinicians are able to monitor this.

In addition, we actually told the clinicians to look very carefully at infections and think about whether there is a differential diagnosis of DKA that can be made. And if there is some thought that there could be, that you actually interrupt, see, and if DKA is confirmed, that you discontinue. So throughout the trial, we have actually changed our monitoring guidelines. And since the patient that passed away, we haven't seen any additional deaths in this clinical trial from DKA, which we believe that through monitoring and very careful attention to glycemic control, you can monitor and manage these patients because DKA is preventable. Thank you.

DR. VASAN: FDA, please?

DR. CHANG: Elaine Chang, FDA. So I think, as he referenced, the onset to DKA in some patients was very late. The median onset was about 9 months. And when we saw the increase in hyperglycemia events, all-grade events, high-grade events, and DKA, compared to the breast cancer data, it suggested that both the exposure to the prednisone with abiraterone and the duration of exposure were factors that increased the risk of these events.

I think your second question was about how we consider the balance of the efficacy and the safety. And I would say that we're not here discussing just the hyperglycemia or just the concerns around toxicity. But it is in the context of this magnitude of treatment effect that makes us question if the benefit-risk is favorable, and that's what we wanted the committee to discuss.

DR. VASAN: Thanks.

Dr. Lee?

DR. LEE: Thank you. Daniel Lee, FDA. If you could please turn to slide 40 of our

presentation. Just to add on to Dr. Chang's point, and then to add on to the sponsor's point, yes, you can increase glucose monitoring. But as you can see on the third row, that's the percentage requiring initiation or change in antihyperglycemic medications. You can see that the difference between the capivasertib arm and the placebo arm is 30 percent. So yes, you can increase and you can be more vigilant, but then you can see that almost 50 percent of patients just needed this big change. So thank you.

DR. VASAN: Dr. Choueiri?

DR. CHOUEIRI: And why is this difference? It's the same dose. Is it the population that is older than the breast cancer? Is it the fact that abi comes with prednisone 5 milligram? Do you think that's all of it, or just men don't -- have more side effects, are less vigilant in taking their glucose?

DR. SUZMAN: Daniel Suzman, FDA. I think we can only speculate, but certainly the addition of prednisone in all patients is different than in the breast cancer setting. Again, the exposure was three

times as long. These are patients who are on ADT, which over time is going to cause metabolic derangements, glucose intolerance. So it may just be a constellation of factors.

DR. FOXLEY: So we do need to remember, as Dr. Suzman has just said, we start from a higher baseline with this population. More of them had diabetes at baseline than the breast cancer population, and they are on background therapies, which in and of themselves can cause metabolic disturbance. So it's not really a level playing field, with regard to hyperglycemia, to compare 291 with CAPItello-281.

DR. VASAN: Thank you.

Dr. Yen?

DR. YEN: Edward Yen from Baylor College of Medicine. I'm sorry to drill down on this more, but I think it's mainly because there's a lot of focus around the population of patients who have an rPFS benefit.

Can you explain a little bit, or give a little bit more clarity -- and this is a question to

the sponsor -- on tumor heterogeneity of PTEN expression within samples? Because the way I'm seeing it right now, these are patients who have de novo metastatic CSPC or HSPC, so the biopsy samples were not likely coming from a radical prostatectomy, of course. So they're going to be coming from a smaller sample. Is PTEN loss something you see consistently throughout the entire tumor sample or is this just a small part?

DR. FOXLEY: I'll ask Dr. Lotan to answer this point. We have an answer for you, I think.

DR. LOTAN: Tamara Lotan. So PTEN loss is a very early event, so if you have loss in the primary tumor, it's typically concordant with all the metastases. Slide 1 up, actually. So it occurs clonally very early on. However, within the primary, you're right that we can get areas of subclonal loss.

This scoring cutoff, which is very stringent, requiring at least 90 percent of cells with loss, sort of enforces that you essentially have clonal loss in the primary in these patients that we call PTEN deficient. So that when we look at

heterogeneity between tumor samples in the same patient, there's very little heterogeneity in terms of the scoring. So we get good concordance, essentially, by enforcing, essentially, that they have clonal loss with the 90 percent cutoff.

Questions to the Committee and Discussion

DR. VASAN: Thank you.

So it's 4:20. We have about 20 minutes for the discussion. I think part of these clarifying questions have bled into discussion, which is, of course, fine. Let me just summarize what we've talked about right until now.

We've focused a lot of these clarifying questions, I think, less on the rPFS and the negative OS, more on the biomarker diagnostic and toxicities. The FDA has asked us to, of course, think about the meaningfulness of this 6-month delta in rPFS. I think that's where we're going to start this conversation.

All right. Yes, I could start. I think, again, we have a positive PFS. We have a negative OS. I do think this biomarker dose response is

interesting. It is an exploratory hypothesis, and I think there's this sense of maybe a creative solution to try to bin in between this 90 percent to 100 percent. Dr. Choueiri asked a lot of questions about dichotomizing the data differently, but at the end of the day, this is an exploratory hypothesis. It sounds like most of the work in the field has really characterized that 90 percent cutoff. There is internal consistency that the sponsor has shown in some data.

Again, the difference between 99 and 100, I don't know how that will play out in the real world, and so that's something that I'm thinking about. I guess to the FDA, it's also just to confirm that this is an exploratory biomarker. This idea of thinking about 93 different than 98 is an exploratory biomarker.

DR. SUZMAN: This is Daniel Suzman, FDA. Yes, we would consider that to be exploratory analyses, again, the way the trial was conducted, the way the diagnostic was validated was with 90 percent, we would consider the additional bins to be

hypothesis-generating only at this point.

DR. VASAN: Thanks. Neil Vasan. Just the last part is, what we also did see is that there is a bit of a dose response in the OS by the higher loss of PTEN. That's sort of, I think, what I'm thinking about right now.

DR. FOXLEY: May I just raise a point of clarification, just something that was stated just now that may be incorrect?

DR. VASAN: Yes, please.

DR. FOXLEY: We heard the OS was negative. I think the summary at the moment is that the OS shows no detriment.

DR. VASAN: Thank you for that clarification.

Dr. Frenkl?

DR. FRENKL: Hi. Tara Frenkl, Bayer Pharmaceuticals, industry rep. What I'm thinking about is a little bit in terms of putting the clinical meaningfulness into context and trying to relay it with the precedent that's been set before and comparing it with those different populations. Because I think it was beautifully framed this

morning about how this is a different, more aggressive population, has a different control, a different time to PFS, much shorter than some of those other populations. And it would be great to hear from some of the clinicians how are they thinking about that, and how is this 7.5 months, in the context of knowing that it's 26, compared to some of the other ones.

DR. HUANG: I'll speak as one of the clinicians. It's a great question, Dr. Frenkl. I think that we are always -- it's appealing to have biomarker driven ideas of how to treat patients upfront. I think we at the VA and other places, obviously ADT plus abi is a backbone of our therapy, and many patients do extremely well on those, but then there are patients who obviously progress very quickly. And I think that is a challenge in our field in terms of trying to find the right therapies and have options for patients upfront. And often times we are using many biomarkers at the upfront setting to treat these men with mHSPC. So I think it's an important consideration.

DR. ROBINSON: I guess we're going around. Kyle Robinson from Penn. I think there's been a lot of discussion about the lack of triplet therapy of docetaxel in the beginning. I think when we're talking about these patients who present with aggressive prostate cancer at the beginning, I do think heavily about docetaxel. You do have to talk to patients about it. I think it's a good drug in a good amount of patients. So I do think about how I would consider that. I think Dr. George spoke to that, that there are some people, we're still just going to go docetaxling (ph), and there are going to be some patients who are still going to be against chemotherapy. And so that's where I do think about that.

I think there are a number of patients who would also be reluctant about insulin shots as well. Some patients really dread that. They think that's almost like a a failure of their control of their own health, not that that's right or wrong, just how people might perceive that. So it's a big discussion about saying we might have another agent, but there's

some other baggage that's going to come with that. I guess that's how I'd frame it.

DR. YEN: I can put in my two cents. Edward Yen from Baylor. I think when you had that initial discussion about triplet versus doublet for a metastatic castration-sensitive prostate cancer patient, guidelines are one thing, and you can sit there and read standard of care options to patients, but it's hard to tell you exactly how the discussion's going to go because every patient's going to have their own preference.

So a lot of the things we've talked about, and what people have said already, goes through that potential discussion that day. You certainly have a lot of people who could refuse chemotherapy, even though you can show them the data with the survival benefit, and the reason could be very various. What people have said earlier today, for example, it may be they're kind of shocked about their diagnosis, and they're still working. They have family to take care of, and they don't really want to be on chemotherapy, even though it might be a standard of care. So that

places the decision making for sure. For a combination like this, for that particular type of patient, it might be actually really important to add to hormonal therapy. But again, the discussion, you could go a lot of different ways, yes.

DR. FRENKL: My takeaway is that it is very individualized, and that this is a separate group of patients that you guys would consider differently.

DR. VASAN: Also, Dr. Rini, I don't know if you had any other thoughts. We've asked all the prostate doctors to weigh in.

DR. RINI: Thank you. Yes. Certainly patients, they don't want chemotherapy. They don't like the word. And this is not just true in the hormone sensitive; it's true in the hormone refractory space. And that's why I asked that question in terms of proven benefit and the survival advantage. The toxicity of this drug and chemo, if you just look at the grade 3, it's about 60 percent. So even though they're different, as Dr. George said, the magnitude is the same, and certainly the duration would be longer with this agent than with chemo. So

I don't know the right answer. I certainly offer chemotherapy triplet to appropriate high-volume patients, and some get it and some don't.

DR. CHOUEIRI: The other thing to remember, with chemotherapy, we stop at a certain number of cycles, 6 to 10, where with this drug, it's continuous until progression.

DR. VASAN: Neil Vasan, NYU. I'll ask one more question to whichever the prostate oncologists want to answer. This is obviously just the toxicity footprint with hyperglycemia and rash. You as a field would have to be talking to your endocrinologists very frequently, your dermatologists very frequently. This is something that in the breast cancer field we had to do with alpelisib. I guess to Dr. Rugo's point, it's certainly gotten better over the years just in terms of the support of oncology management, but it is something that will have a footprint in the field, both in academia and, then, as well as in the community.

So I'm wondering if you could speak to any of these unique side effect types of management,

especially noting from the FDA's presentation, of course, that so many of these therapies are different antiandrogens or chemo, which obviously are totally different drug classes.

Dr. Yen?

DR. YEN: Yes. Sorry. I wasn't sure if it was directed to any particular person. I would just say the toxicities are important to take into consideration, but it's unrealistic to expect that -- let's say, for example, the patient who gets DKA from the combination, we're not going to keep them on the same regimen to have them experience DKA over and over and over and over, right? So ultimately, when that first event happens, and hopefully it's not DKA, but if it starts to get out of control, realistically, we'll have to get in contact with whoever, an endocrinologist or PCP, whoever it is to help get the blood sugar under control. If they can't get it under control, then, ultimately, the patient will have to discontinue therapy.

So I think that's important to take into

account. For example, in GU oncology, we have a lot of other medications that we balance that do have significant side effect risk, like say, for example, checkpoint inhibitors, TKIs with RCC. I mean, all of those have significant AE profiles, and we manage them. And I think the mix of the things that we're seeing and explained here today -- rash, diarrhea, hyperglycemia -- generally those fall in the category of things that we can manage.

DR. VASAN: Dr. Choueiri?

DR. CHOUEIRI: But this is a population of elderly men, where the risks are higher than what's seen with this drug in breast cancer. I have concern about the use of insulin here. It's not as simple as it is. I would like to see an analysis of health utilization when someone starts going on insulin, with everything that comes net, the glucometer, the strips, the phone call. It is a problem. Now, we tend to move fast to insulin compared to oral therapies in oncology, but also that's a problem. An analysis, back of the envelope, since we started doing this, 1 in 8 or 10 patients might be on

insulin, every almost grade 3 hyperglycemia.

DR. VASAN: Are there any other discussion points that anyone on the ODAC panel would like to bring up? Dr. Robinson?

DR. ROBINSON: Can we clarify that? I thought Dr. George had reported there was actually long-term insulin, which is 3 percent. Do they have the data for who remained on insulin versus who just needed it acutely?

DR. VASAN: Could we ask the sponsor to clarify?

DR. FOXLEY: Yes. Most patients required short course. I'll ask Dr. Patel to describe that to you.

DR. PATEL: In patients who had an adverse event of hyperglycemia, the duration of insulin was actually quite short. And after discontinuation, only 3.3 percent of patients actually remained on insulin, which suggests that the hyperglycemia and associated insulin use, actually diabetes is reversible in these patients. And I think that's a very important point, that you can discontinue

therapy and you don't have to keep the patients on insulin long term. Thank you.

DR. VASAN: Dr. Yen? And then I'll give Mr. Conway the last word.

DR. YEN: Okay. Yes. I think one thing that's really stuck out to me this entire day so far is that we're really dealing with a different patient population. Even though they all kind of share the same prostate cancer category, as people have explained already, all prostate cancer is not necessarily the same.

The person who I see as the prototypical person with a PTEN loss, potentially, would be a younger patient with really aggressive metastatic presentation. So this is not your 70-plus-year, 75-year-old gentleman with low-volume metastatic recurrent cancer, where they have diabetes, hypertension, cholesterol. I mean, this could potentially be a 40, 50, 60 year old. I think the average age on the trial was actually 67. So that's certainly younger, and the risk-benefit calculus is different for those patients, specifically with that

particular molecular profile.

DR. VASAN: Mr. Conway?

MR. CONWAY: Thank you very much. So these are the things that I think about as I listen to this. I think there is a distinct patient population. I think the status quo is inadequate in terms of the tools that the doctors have to work with the patient and actually engage in informed decision making about all of their options.

It's interesting listening to my colleagues around the table about how they would each tailor a conversation to a particular patient, on a particular day, given the patient's particular concerns. I don't think you can listen to today's conversation and not think in terms of those who need to keep working in part-time or full-time jobs that are meaningful to them, birthdays, travel, graduation, economic security. Some might dismiss 6 or 7 months.

I don't know who would do that, actually, because the calculations that patients make, especially if you're a high-risk patient, they're pretty personal. And if you find a healthcare

professional who's willing to work with you and has the tools in the toolbox, that's deeply meaningful. Is it clinically meaningful? Well, I think you have to road test that with patients. I don't think you leave it to just doctors, quite frankly. Because if you're talking to a patient, you're talking to a family, and oftentimes you're talking to a community. And these are decisions that this particular patient population should have patient-care choice and be able to make with doctors they choose and they trust.

We talked about some of the side effects not directly related, of course. But if you have an organ transplant, you deal with immunosuppression. I've dealt with it for 29 years. I've taken over 179,000 pills. I've had a lot of conversations about side effects, and many of those discussed here. Patients are pretty smart. They can figure it out. They're also pretty smart about healthcare utilization, what adds to the system and what doesn't, and that gets calculated into the trade off and the benefit to them of delaying disease progression and staying in the arena of life.

And I put that out to you because I think the bigger picture here, and the true north in this discussion, has to be the patients. They are the most important stakeholders in the discussion, not industry, and not necessarily government. You have to achieve a standard of safety, and that's the FDA's job. But for the safety issues that we've discussed, I'm not certain how many patients that are in a tough situation haven't already had those conversations at some point, or will have those conversations as they go forward. So thank you.

DR. VASAN: Thank you, Mr. Conway.

So I'll just do a quick summary. On one hand, we have a trial that has met its primary endpoint for rPFS but some issues certainly when comparing this registrational trial to prior practice-changing, registrational trials in prostate cancer. On the other hand, we've heard some conversations that there may be some distinct populations of patients that may benefit, either populations based on their PTEN IHC, populations based on symptom management and maybe patients

seeking different types of therapies, and a desire for shared decision making to reconcile this. So I think that's going to be the tensions that we're thinking about in this vote.

So now that the discussion portion has ended, we will turn our attention to the task at hand, which is the careful consideration of the data before the committee, as well as the public comments. We will proceed to the questions to the committee. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate at the specific request of the panel.

So we will now proceed to our question, which is a single voting question. We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you 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.

I realize I didn't read the voting question, which I probably should do. So the question is, based on the CAPItello-281 results, does the benefit of adding capivasertib to abiraterone and prednisone outweigh the risk for the proposed indication?

Does anyone have any questions about the wording or any comments about the question?

(No response.)

DR. VASAN: All right. Please press the button firmly that corresponds to your vote. The vote will go into the record, and next, we will go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. We will continue in the same manner until all questions have been answered or discussed.

All right. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote or you wish to change your vote, please

press the corresponding button again before the vote is closed.

(Voting.)

DR. FRIMPONG: Dr. Gradishar, we are awaiting your vote by e-mail.

DR. GRADISHAR: I sent it.

DR. FRIMPONG: Alrighty, everyone. Please bear with us as we tally the votes.

(Pause.)

DR. GRADISHAR: Do you have it?

DR. FRIMPONG: I see it on my end. I'm communicating with the AV team.

(Pause.)

DR. FRIMPONG: Joyce Frimpong, Designated Federal Officer. For the record, ere are 7 yes, 1 no, and 1 abstain.

DR. VASAN: Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record.

DR. CHOUEIRI: Toni Choueiri, Dana-Farber,

Boston. This was a way tougher decision than the morning, at least for me. I voted actually yes, and this was definitely not an easy vote. I think Mr. Conway at the end -- and interesting enough it was the last comment -- has put it very well. I think the evidence demonstrates this is a statistically significant trial. It's absolutely biologically plausible.

The problem I had is the PTEN loss definition. I'm glad that the folks at the FDA had the answers ready for me. If you exclude the 99 and the 100, the PFS hazard ratio is 0.94, and for OS, it crosses 1. However, for a patient, and that is 10 percent of all patients will have 99 and 100, how can they receive this targeted treatment if we don't approve it?

I actually agree with Dr. George. Have it there and let the physician discuss it with the patient. Nevertheless, I'm really worried that it will be given, if approved, in that condition, in patients 90 percent or more. So the FDA, I implore the agency that the approval will be in those

40 percent, 99 to 100, because this drug has side effects. So my vote has been yes for that reason. Thank you.

DR. VASAN: Neil Vasan, NYU Langone. I voted yes. I felt that, overall, the totality of the data suggested clinical efficacy, clinical meaningfulness. I think that the term "clinical meaningfulness," of course, we think about the primary endpoints, but we also think about how this drug would be deployed in the real world. And I think that the conversation we had, certainly around toxicities, was convincing that this is not only something that we as a field can manage, but also something that would be tailored individually for a patient with individual conversations.

Make no mistake, this will be challenging. I'm not convinced the diagnostics, yet, have been optimized. And for toxicity management, we will have to be enlisting our endocrinology and dermatology colleagues as we have in breast cancer for PI3-kinase pathway inhibitors. But those are the reasons that I voted yes. Thank you.

DR. HUANG: Franklin Huang, UCSF. I voted yes. I think, yes, that the totality of the evidence and trying to understand and balance the benefits and risks, and then this patient population, which has unmet need, convinced me that this was significant enough to vote yes for it. I do think there are areas for optimization and consideration for the FDA as well. And at least for the hyperglycemia that we talked about, the insulin issues, I hope that in a post-GLP1 world, that we may be better at managing it, But I think there are other toxicities here that we did cover, and that we should also be mindful of. And I hope that in the real-world deployment of this medication, should it get to patients, will benefit many. So that's my vote.

DR. GRADISHAR: Bill Gradishar, Northwestern. I voted yes. I think, again, my impression is that the 7-plus months is meaningful. I don't think this will be a therapy for everybody, and I think the breast cancer experience doesn't perfectly mirror what has been experienced in this trial. It's longer duration, different population. Nonetheless, I think

as physicians become more acquainted with the drug and the management, for the right patient, this could have a meaningful outcome. So I voted yes.

DR. RINI: Brian Rini, Vanderbilt. I voted no. This was a really difficult vote, as I think people have said. I think I was swayed mostly by what I perceived as a relatively marginal benefit and the magnitude and duration of toxicity. And I think, especially on the benefit side, the guidance from the FDA around what they consider clinically meaningful, that was sort of a context setter for me. And so, again, I think it was really close. I think there's a lot to work out. But I voted no.

DR. ROBINSON: Kyle Robinson, Penn. So I voted yes, basically just answering the question in front of me, did the benefit outweigh this risk? Like everyone has now discussed, with a lot of new cancer therapies, specifically immunotherapy, we've had to work with all of our different specialties in managing the different effects we're causing, adding different drugs, and so we're used to that world now. And like Dr. Choueiri said, there is a small group of

patients who I think this drug will be for, that I'll reach for. So that's how I voted.

DR. YEN: Edward Yen from Baylor College of Medicine. I think this was a very difficult decision for me, kind of wavered back and forth, actually, throughout this day. But I think there were a couple of things that really stood out to me in my vote for yes, one of which is that I really did like the fact that there was a stratified PTEN expression with rPFS and OS. I think that demonstrates and confirms more of the clinical activity to this target.

The other thing is trying to extrapolate from science and trial findings to clinical practice and meaningfulness to our patients. I definitely agree that I don't think this drug will necessarily be for everybody, but there are definitely going to be some cases -- I can already see in my head -- some other patients who could potentially benefit quite a lot. And maybe the half year's worth of rPFS benefit may not be that meaningful for some patients, but could certainly be a lot more meaningful to other patients. But that's part of the reason why I voted yes. I

think there's a lot of work to be done, though.

DR. BALLMAN: Karla Ballman. I abstained. And it has to be the first time in my life I've ever abstained from a vote, so I didn't take it lightly. Where I was coming down, and I was squarely on the fence, was there was an improvement in rPFS and it was statistically significant. Even if the p-value is very close, that's not what statistical significance means. So I did see that. And I also like offering more choices for physician and patients to make combined decisions.

Where I came down on the other side, though, it sounds like there has to be intense monitoring, and I worry about out in the real world -- not my esteemed colleagues that I work with in academic centers -- what it might look like, and what some of the risks might be, if it may be even more and outweighs that benefit that is there. So that's where I fell. I don't know, so I decided I would defer to my clinical colleagues to make the ultimate decision.

DR. VASAN: Thank you.

And Mr. Conway?

MR. CONWAY: Thank you. Paul Conway. I voted yes. And the reason why I voted yes was because I believe the sponsor met the endpoint. It's evidence based. I believe it creates greater patient care choice. And also, that it is not for every single patient, clearly, but this is where the issue of trust in the medical profession comes in and the doctors that patients choose.

The other thing I would say is that I agree that the education is really going to matter on this and that the onus has not been removed from industry. To make certain, the information that they provide to patients, while it may be clear and written for clinicians, they should also be writing materials for the patient community at a grade level that is understandable and encourage questions to be asked, because that's only fair to the patient population. But my vote yes is an indication that there's a distinct patient population in need of innovation, and part of FDA's job is to advance safe innovation and to clearly communicate the risk.

I also believe, with all due respect, that the terminology of "clinically meaningful" by the FDA needs to evolve. And it needs to evolve quickly to be in pace with patient populations that are becoming more and more distinct as medicine, and science, and research advances, and we can identify these specific groups of patients that may benefit from new therapy pathways. Thank you.

DR. VASAN: Thank you.

Before we adjourn, are there any last comments from the FDA?

DR. SUZMAN: Daniel Suzman, FDA. I just want to thank the panel for an excellent discussion. We very much appreciate your input. We'll take it under under advisement, and thank you for your time.

Adjournment

DR. VASAN: We will now adjourn the meeting. Thank you.

(Whereupon, at 4:53 p.m., the afternoon session was adjourned.)