FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC)MEETING

Virtual Meeting

Friday, April 28, 2023

11:00 a.m. to 4:07 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

She-Chia Jankowski, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Mark R. Conaway, PhD

Professor, Division of Translational Research and

Applied Statistics

Department of Public Health Sciences

The University of Virginia School of Medicine

Charlottesville, Virginia

Jorge A. Garcia, MD, FACP

(Chairperson)

Chief, Division of Solid Tumor Oncology

George & Edith Richman Distinguished Scientist

Chair

Professor of Medicine and Urology

GU Medical Oncology Program

University Hospitals Seidman Cancer Center

Case Comprehensive Cancer Center

Case Western Reserve University

Cleveland, Ohio

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Associate Professor of Medicine

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(Non-Voting)

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(Acting Industry Representative)

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Pyxis Oncology

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(11:00 a.m.)

Call to Order

DR. GARCIA: Good morning, and welcome. I would first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Lauren-Jei McCarthy. Her email is currently displayed.

My name is Dr. Jorge Garcia, and I will be chairing today's meeting. I will now call the April 28, 2023 Oncology Drugs Advisory Committee meeting to order. The agenda for this meeting is currently displayed. Dr. She-Chia Jankowski is the designated federal officer for this meeting and will begin with introductions. We will first start with the standing members of the ODAC.

Dr. Jankowski?

Introduction of Committee

DR. JANKOWSKI: Thank you, Dr. Garcia.

Good morning. My name is She-Chia Jankowski, and I am the designated federal officer, DFO, for this meeting. When I call your name,

please unmute yourself and turn on your camera. Please introduce yourself by saying your name and affiliation, for the record.

We'll first start with ODAC members.

Dr. Conaway?

DR. CONAWAY: Mark Conaway, biostatistics, University of Virginia.

DR. JANKOWSKI: Dr. Garcia?

DR. GARCIA: Jorge Garcia, professor of medicine and urology, and the chair of Solid Tumor Oncology at University Hospitals Seidman Cancer Center, Case Western Reserve University in Cleveland, Ohio.

DR. JANKOWSKI: Dr. Lieu?

DR. LIEU: Good morning, everybody. I'm Chris Lieu. I'm an GI medical oncologist at the University of Colorado Cancer Center and serve as the associate director for clinical research.

DR. JANKOWSKI: Dr. Madan?

DR. MADAN: Good morning. My name is Ravi Madan. I'm a medical oncologist. I head the prostate cancer clinical research section here at

the National Cancer Institute in Bethesda, Maryland.

DR. JANKOWSKI: Mr. Mitchell?

MR. MITCHELL: I'm David Mitchell. I'm the consumer representative to the ODAC. I am the founder of an organization called Patients for Affordable Drugs, and I'm a multiple myeloma patient myself.

DR. JANKOWSKI: Dr. Nieva?

DR. NIEVA: Hello. This is Jorge Nieva. I'm the section head of solid tumors at the University of Southern California Norris Comprehensive Cancer Center.

DR. JANKOWSKI: Dr. Rosko?

DR. ROSKO: Good morning. I'm Ashley Rosko. I'm an associate professor in the Division of Hematology at The Ohio State University and medical director of the oncogeriatrics program at the James Comprehensive Cancer Center.

DR. JANKOWSKI: And Dr. Vasan?

(No response.)

DR. JANKOWSKI: Dr. Vasan, please unmute

yourself.

DR. VASAN: Hi. This is Neil Vasan. I'm unmuted, but I can't seem to start my video, but I'll introduce myself.

Good morning. My name is Neil Vasan. I'm a physician/scientist and breast oncologist at Columbia University Irving Medical Center in New York City.

DR. JANKOWSKI: Thank you.

Next is the acting industry representative, Dr. Bui.

DR. BUI: Good morning. I am Dr. Michael Bui. I'm a senior vice president of Global Regulatory Affairs with Pyxis Oncology.

DR. JANKOWSKI: Then we have temporary members.

Dr. Bitting?

DR. BITTING: Good morning. My name is Rhonda Bitting. I'm a medical oncologist/staff physician at the Durham VA hospital and an associate professor of medicine at Duke University.

DR. JANKOWSKI: Dr. Graff?

DR. GRAFF: Hi. My name is Julie Graff. I am a medical oncologist, a professor of medicine at Oregon Health and Science University in Portland Oregon, as well as at the VA Portland Health Care System.

DR. JANKOWSKI: Dr. Harzstark?

DR. HARZSTARK: Good morning. My name is Andrea Harzstark. I am a GU medical oncologist at Kaiser Permanente in San Francisco, California and co-director of the national GU oncology program for Kaiser Permanente.

DR. JANKOWSKI: Mr. Kungel?

MR. KUNGEL: I'm Terry Kungel, and prostate cancer came into my life when my paternal grandfather was diagnosed. When I was 16, I was a pallbearer at his funeral. When I was 17, my dad died from prostate cancer, and I was diagnosed in 2008. I've been involved with the Maine Coalition to Fight Prostate Cancer.

DR. JANKOWSKI: Thank you.

And Doctor Rini.

DR. RINI: Good morning, everyone. Brian

Rini. I'm a GU medical oncologist and chief of clinical trials at Vanderbilt-Ingram Cancer Center in Nashville.

DR. JANKOWSKI: Finally, we have FDA participants.

Dr. Pazdur?

DR. PAZDUR: Richard Pazdur. I'm the director of the Oncology Center of Excellence here at the FDA.

DR. JANKOWSKI: Dr. Kluetz?

DR. KLUETZ: Hi. My name is Paul Kluetz. I'm a medical oncologist and the deputy director of the Oncology Center of Excellence here at the FDA.

DR. JANKOWSKI: Dr. Amiri-Kordestani?

DR. AMIRI-KORDESTANI: Hi. My name is Laleh Amiri-Kordestani. I'm the division director for the Division of Oncology 1.

DR. JANKOWSKI: Dr. Suzman?

DR. SUZMAN: Daniel Suzman. I'm a medical oncologist and deputy director for the Division of Oncology 1.

DR. JANKOWSKI: Dr. Weinstock?

DR. WEINSTOCK: Hi. I'm Chana Weinstock. I'm a medical oncologist and acting supervisory associate director for the Division of Oncology 1.

DR. JANKOWSKI: And Dr. Fallah?

DR. FALLAH: Good morning. I'm Jaleh Fallah, a medical oncologist and clinical reviewer at FDA.

DR. JANKOWSKI: Thank you. That concludes it. I'll hand it back to you, Dr. Garcia.

DR. GARCIA: Thank you, Dr. Jankowski.

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, a gentle reminder; individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine

Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

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

Dr. Jankowski will now read the Conflict of Interest Statement for the meeting.

Dr. Jankowski?

Conflict of Interest Statement

DR. JANKOWSKI: Thank you, Dr. Garcia.

The Food and Drug Administration, FDA, is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the

committee are special government employee, SGEs, or regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed

likely to affect the integrity of the services which the government may expect from the employee.

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

Today's agenda involves the discussion of supplemental new drug application, sNDA, 208558/S-025, for Lynparza, olaparib, tablets, submitted by AstraZeneca Pharmaceuticals, LP. The proposed indication -- use -- for this product is in combination with abiraterone and prednisone, or prednisolone, for the treatment of adult patients with metastatic castration-resistant prostate cancer, mCRPC. This is a particular matters

meeting during which specific matters related to AstraZeneca's sNDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue. With respect to FDA's invited industry representative, we would like to disclose that Dr. Michael Bui is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Bui's role at this meeting is to represent industry in general and not any particular company. Dr. Bui is employed by Pyxis Oncology.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on

the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committees of any financial relationships that they may have with the firm at issue. Thank you.

Back to you, Dr. Garcia.

DR. GARCIA: Thank you.

We will now proceed with the FDA introductory remarks from Dr. Chana Weinstock.

Dr. Weinstock?

FDA Introductory Comments - Chana Weinstock

DR. WEINSTOCK: Thank you.

Good morning. My name is Chana Weinstock, and I'm a medical oncologist and team leader for this application. Today we will be discussing olaparib in combination with abiraterone for metastatic castration-resistant prostate cancer or mCRPC.

Olaparib is a PARP inhibitor, part of a

class of drugs that exploit synthetic lethality and target DNA repair defects in cancer cells. Homologous recombination repair, or HRR, is an essential pathway for DNA repair. Several genes are involved in this pathway, including BRCA1 and BRCA2.

PARP inhibitors are approved for treatment of prostate cancer as a single agent in a later line of therapy. Olaparib is restricted to patients who have HRR mutated tumors, approximately 20 percent of patients. BRCA represented the most prevalent and the most PARP-sensitive mutation in the olaparib approval. Rucaparib is another PARP inhibitor also approved in later lines of therapy in prostate cancer for patients whose tumors harbor BRCA mutations.

This application would represent the first approval of a PARP inhibitor for a broad population of patients with prostate cancer unselected for BRCA or HRR mutations. Despite the increasing use of androgen receptor pathway inhibitors in the hormone-sensitive setting, this would be a large

number of patients, as about 45,000 patients are diagnosed with mCRPC annually.

This is an early metastatic setting where most patients are either asymptomatic or minimally symptomatic from their cancer. The addition of olaparib here needs to be considered in the context of multiple available treatment options, including abiraterone monotherapy, which is generally well tolerated with long duration of treatment and expected survival.

The data on which this application is based is obtained from PROpel, a randomized phase 3 trial of abiraterone plus olaparib or placebo in patients with mCRPC, of whom about 70 percent had mild or no pain at baseline. The primary outcome measure was radiographic progression-free survival or rPFS. Overall, survival was a secondary endpoint.

PROpel enrolled an intent-to-treat population that included all patients, regardless of BRCA or HRR mutation status, unstratified by mutation status with no alpha-controlled analysis plan for these subgroups. We would consider this

trial design inappropriate today. Given emerging data on the strength of BRCA mutations as predictive biomarkers for PARP inhibitors, BRCA status should have been prospectively evaluated with efficacy results analyzed separately for biomarker selected subgroups; for example, with stratification or enrollment into separate cohorts. This is a significant design flaw that other sponsors designing similar studies have more appropriately addressed, and we would be rewarding poor trial design if we disregarded this issue.

PROpel met its primary endpoint, with an 8-month improvement in median rPFS and a non-significant trend towards improvement in overall survival. In general, FDA has considered rPFS, similar to PFS, but which includes new lesions on bone scans, in addition to soft tissue progression on CT scans, to be a clinical endpoint; that with sufficient magnitude of improvement may be acceptable as the basis for traditional approval if supported by consistency of other clinically meaningful endpoints like overall survival and

acceptable safety.

So why, with an 8-month improvement in rPFS and a hazard ratio for overall survival that does not at face value raise concerns for potential detriment, are we discussing this application in front of ODAC? FDA's concerned that the potential benefit from the addition of olaparib to a known, highly effective therapy, abiraterone, may be restricted to a small subset of the overall population, those with tumor BRCA mutations; while there may be modest efficacy, and even the potential for harm, in the much larger population of those in whom no BRCA mutation can be identified.

The related question for discussion over the course of the ODAC would also be, what magnitude of rPFS improvement would be considered clinically meaningful in the absence of an overall survival improvement in an add-on trial design in this setting?

Multiple studies in prostate cancer and in other tumors, such as ovarian and breast cancers,

have demonstrated that PARP inhibitors work very well in patients whose tumors harbor BRCA mutations with much less efficacy in those who do not; however, PROpel enrolled a heterogeneous patient population regardless of BRCA mutation status. Patients' mutation status was retrospectively determined by testing of ctDNA and tumor tissue, and was therefore not included as a stratification factor for randomization. There was no prespecified formal testing for subgroup analysis, based on BRCA mutation status. As mutations in BRCA genes have been demonstrated to be the primary sensitizing mutations in other trials of PARP inhibitors, we performed a post hoc subgroup analysis of PROpel by BRCA status.

Here we see the overall efficacy results in terms of rPFS and OS hazard ratio for the ITT population in PROpel, and the ITT population is represented here by this bar graph. There appears to be strong efficacy both in terms of rPFS and overall survival in the small proportion of patients, 11 percent of the ITT population, with a

mutation in BRCA by either tumor tissue or circulating tumor DNA. Here at the bottom of the screen in the green box are the rPFS and overall survival results for this subgroup with BRCA mutations, which shows a hazard ratio of 0.24 for rPFS and a hazard ratio for overall survival of 0.3.

What we also see is that for the 54 percent, which is over half of the ITT populations with no BRCA mutation confirmed by both ctDNA and tumor tissue testing, represented here by the red portion of this bar graph of the overall population, in these patients, there appears to be very attenuated rPFS benefit and no benefit, or even a potential detrimental effect, on overall survival. Again, the rPFS and overall survival results for these patients are here in the red box, including a hazard ratio for overall survival of 1.06 in the subgroup, representing a potential OS detriment.

Now the other patients represented here by the yellow box are 35 percent of the ITT, and likely due to difficulty getting adequate tissue

for testing in this setting or bone metastases predominate, have overall indeterminate test results or what we're calling undetermined BRCA status. The majority of this subgroup had negative results for BRCA ctDNA but unknown results by tumor tissue testing, largely related to tissue quality or other assay issues.

We note that had the trial required prospective evaluation for BRCA status, this population would likely have been better determined as being either BRCA mutated or non-BRCA mutated. In these patients, results for both rPFS and overall survival appear to be intermediate between the populations of BRCA mutated and non-BRCA mutated. This subgroup is probably a mixture of some of the green and some of the red groups, with a lot of heterogeneity.

Here are the Kaplan-Meier curves for OS, where olaparib is red and placebo is blue, based on the three subgroups that I just presented. In particular, the right figure for the non-BRCA-mutated subgroup shows that the two curves are

close together and that the placebo arm in blue is above the olaparib arm in red for the first approximately 24 months.

Let's take a close look at the BRCA testing used in PROpel. ctDNA is very good at ruling in a BRCA mutation, but not as good at ruling one out. ctDNA testing only identifies 74 to 80 percent of BRCA mutations, identified with tumor tissue testing, which is the basis of the recommendation in prior approvals that those with a negative ctDNA test have a reflex tumor tissue test. So it's possible that a small percent of patients with negative ctDNA and unknown tumor tissue testing, in that 35 percent of patients I just showed you, have undetected BRCA mutations.

Based on the known performance of the ctDNA assay in patients with evaluable paired tissue samples and the prevalence of BRCA mutations in this and other studies, a small percentage of these undetermined patients may actually be harboring an undetected BRCA mutation and could potentially benefit from olaparib. However, this group also

includes a much larger population of patients, likely over 90 percent, who are likely to be truly BRCA negative. These patients would be exposed to the harms of add-on therapy, which I'll discuss later, with relatively little likelihood of efficacy. So it's concerning to treat all these patients in this heterogeneous subgroup without knowing who the patients with BRCA mutation are.

Considering the population of patients without a documented tumor BRCA mutation as one group, the improvement in median rPFS by investigator compared to abiraterone alone was only 5 months, and there was no evidence of an overall survival benefit. This 5-month improvement on its own is likely of dubious clinical benefit in this setting, especially given the disease setting with prolonged life expectancy of patients, and particularly in the context of a treatment duration of 20 months in the olaparib arm. So again, the patients are receiving 20 months of therapy to get a 5-month improvement in rPFS.

We note that the magnitude of rPFS

improvement here was larger per blinded review, which was a secondary endpoint; however, FDA considers this to represent an overestimation of the true magnitude. This will be discussed further in the second FDA presentation.

One of the reasons that PROpel was designed without stratification by HRR or BRCA mutation was due to early results from a previous small exploratory study conducted by the applicant in the second-line mCRPC population called Study 8. With a similar design to PROpel but a much smaller sample size, this study randomized patients with mCRPC unselected for BRCA or HRR status to abiraterone plus either olaparib or placebo and did not stratify for mutation status. The primary endpoint of the study was rPFS by investigator assessment.

Here are the initial study results in the ITT population, which appears similar to the results of PROpel. The rPFS results per investigator, available at the time of the design of PROpel, appeared similar regardless of HRR

status, and the sponsor wanted to submit these results for an all-comer population for accelerated approval, but FDA discouraged submission based on many concerns, including the heterogeneous and unstratified trial population.

When PROpel data were submitted, the applicant also resubmitted Study 8 results and initially also requested inclusion of Study 8 efficacy results in product labeling for olaparib; however, this time we had a chance to look at blinded review of rPFS results and also the three groups by BRCA status that we used for analysis of the PROpel results.

When analyzing Study 8 this way, a similar pattern emerges to the the PROpel data, with particular concern about causing harm to patients with non-BRCA-mutated tumors in terms of rPFS and OS, as you can see here in the red box, with hazard ratios that are well above 1 for rPFS and overall survival, including an overall survival hazard ratio of 2.77. This adds to our concern about possible harm in patients with non-BRCA-mutated

tumors, this time from a second randomized trial with data external to PROpel data.

Let's go back to PROpel and look at safety. I want to emphasize that this is an early line of therapy, generally a minimally symptomatic population, so toxicity may be particularly meaningful to patients given duration of treatment and compared to the generally well-tolerated monotherapy of abiraterone. On PROpel, there were increases in the olaparib arm in serious and high-grade toxicity, as well as fatal reactions with substantially increased rates of myelosuppression, GI toxicity, and venous thromboembolism.

Almost 1-in-5 patients on olaparib required a transfusion for anemia, and these thromboembolic events were pulmonary emboli in two-thirds of cases. These toxicities are not occurring in highly symptomatic patients with refractory metastatic disease without alternative options; again, these are patients with fairly minimal disease-related symptoms at baseline.

To again emphasize the population at issue here, this is a large population fairly early in the disease course who'd receive this combination for a long time with median duration of exposure of 20 months on the olaparib-plus-abiraterone arm. Patients and their oncologists may not know whether the olaparib was ineffective, as it is paired with abiraterone, a very effective therapy. So in patients without BRCA mutations, a much larger population than those who have BRCA mutations, there's the potential that olaparib is a toxic placebo with exposure for a prolonged duration without demonstration of futility.

This is different than a monotherapy setting, where lack of efficacy may be clear much earlier, and therapy could be stopped for early disease progression. Thus, the risk-benefit analysis and considerations for optimal patient selection are different for an add-on therapy like this.

We generally discourage use of post hoc subgroup analyses in trials to argue for efficacy

in a specific group, particularly in a failed trial; however, given the results and consistency across trials that BRCA is a strong predictive biomarker for PARP inhibitor efficacy, we're concerned that safety and efficacy has not been demonstrated for the non-BRCA population, and this is confirmed by external findings in other trials of PARP inhibitors in ovarian and prostate cancer.

The burden of proof is on the applicant to demonstrate efficacy and safety in the whole indicated population in the well-designed trial. That's very different than trying to rescue a trial with efficacy in an un-preplanned subgroup based on post hoc analysis, which is what we discourage.

There's precedent for limiting use of a drug based on post hoc analysis in a subgroup with possible compromised safety or overall survival detriment, including such examples as KRAS mutation in colon cancer and squamous histology in non-small-cell lung cancer. FDA guidance specifically states that if a trial demonstrates benefit only in patients in a selected subgroup, FDA may limit the

indication to a narrower population than the original broad population enrolled overall.

To reiterate, this application can be viewed as part of a broader conversation on PARP inhibitors in populations negative for HRR or BRCA mutations. We've seen, with longer follow-up of maintenance use of PARP inhibitors in ovarian cancer, that potential overall survival detriments in mutation-negative patients have emerged, leading to recent restriction of previously broad approvals to BRCA mutation populations only.

We also see in the MAGNITUDE trial of a PARP inhibitor in prostate cancer, which did pre-screen and stratify by HRR and BRCA mutation status, allowing better determination of efficacy and safety in the non-mutated population if the non-HRR cohort was stopped early for futility. However, we do realize that PROpel was designed early, before trials were designed with stratification and prespecified analyses by BRCA mutations. Our experience with PARP inhibitors in this disease and other disease settings has taught us the need to

account for these considerations in trial designs, and this is now something that we strongly recommend.

In summary, PROpel demonstrated a statistically significant rPFS improvement in the ITT population attributable to BRCA mutation as in other trials of PARP inhibitors. As certainty regarding absence of BRCA mutation increases, rPFS appears to decrease. We're concerned about a potential OS detriment in patients with non-BRCA-mutated tumors, which makes up more than half of the ITT population. This is based on an overall survival hazard ratio of 1.06 in this population in PROpel.

Study 8 also shows lack of benefit and potential OS detriment in the non-BRCA-mutated population. This includes a hazard ratio for overall survival of 2.77 in this population in Study 8. Patients with non-BRCA-mutated tumors are at risk of prolonged exposure to toxicities of olaparib.

Despite lack of prespecified analysis for

the BRCA-mutated and non-mutated populations with either a separate cohort or stratification, which in retrospect should have been integral to the study designed, PROpel demonstrated modest rPFS improvement and potential harm in populations with high confidence for lack of BRCA mutation. This finding is consistent across trials of PARP inhibitors in prostate and other tumor types.

Here's the voting question that we'd like the advisory committee members to consider. As FDA reviews the proposed indication for olaparib in combination with abiraterone for initial treatment of mCRPC, should the indication be restricted to patients whose tumors have BRCA mutation? If you feel the combination should not be approved at all, please abstain from voting and explain your thinking regarding approvability during the post-voting discussion period. Thank you for your attention.

DR. GARCIA: Thank you, Dr. Weinstock.

Both the Food and Drug Administration, FDA, 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 applicants, including the AstraZeneca Pharmaceutical, LP's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant, such as consulting fees, travel expenses, honoraria, and interest in the applicants, 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 AstraZeneca

Pharmaceuticals, LP's presentation.

Applicant Presentation - Cristian Massacesi

DR. MASSACESI: Good morning, members of FDA and the Oncology Drugs Advisory Committee. My name is Cristian Massacesi, and I am AstraZeneca's chief medical officer and oncology chief development officer. The focus of today's discussion is Lynparza, also called olaparib, in combination with abiraterone and prednisone, or prednisolone, for the treatment of adult patients with metastatic castration-resistant prostate cancer. Currently, this indication is approved in 37 countries around the world. Olaparib was first approved in the United States in 2014 and is approved across four tumor types.

Olaparib was first approved as a monotherapy in a biomarker-selected population based on the phase 3 PROfound study. Today we will discuss a different development approach, olaparib in combination with abiraterone in an all-comer population. This was based on the phase 2 proof-of-concept Study 8, which demonstrated the

clinical benefit of the combination in patients with mCRPC irrespective of a biomarker status. Subsequently, PROpel was designed as a pivotal phase 3 study in an all-comer mCRPC population. A Type B meeting was held with FDA in May 2018 to discuss and agree on key study design elements, including the patient population, primary and secondary endpoints, eligibility criteria, and the multiplicity testing procedure.

A mechanistic rationale for the combination in all-comers is based on the fact that the androgen receptor in PARP are both important for the repair of DNA damage in prostate cancer cells. Olaparib is a PARP inhibitor that not only prevents DNA repair but also traps PARP onto the DNA, resulting in induction of DNA damage. The androgen receptor facilitates DNA repair, and its binding to damaged DNA is dependent on PARP.

Olaparib and abiraterone together will therefore more effectively inhibit the androgen receptor-dependent DNA repair. The greatest effect of the combination will be seen in BRCAm prostate

cancers, but even in prostate cancer cells without BRCA or other HRR mutation, the combination of olaparib and abiraterone will result in increased DNA damage and more effective anti-cancer activity.

Here are some of the supportive preclinical data showing that the combination effect is seen even in non-BRCAm and non-HRRm tumors. First, in response to the induction of DNA damage in a non-BRCAm and non-HRRm prostate cancer cell, the androgen receptor binds efficiently to DNA to repair it. This binding is inhibited in the presence of olaparib. Second, in a metastatic non-HRRm prostate cancer model, the combination of olaparib and NHA demonstrates a greater level of DNA damage. And finally, increased anti-tumor activity for the combination was observed in an in vivo model non-BRCAm, non-HRRm.

The results of two randomized-controlled trials supported the mechanistic rationale for olaparib and abiraterone in an all-comer mCRPC patient population. The phase 2 Study 8, that established the dose and demonstrated the proof of

concept in an all-comer population with no evidence that HRRm was a predicted biomarker, and the pivotal phase 3 study, PROpel, an all-comer study, will be the focus of today's presentation.

Following my comments, Dr. Neal Shore will present the disease background and unmet needs in mCRPC, a fatal disease with no meaningful improvements in first-line treatment outcome since the approval of NHA in almost 10 years ago. Dr. Laurence Toms will discuss efficacy and show that PROpel was a positive study in an all-comer population and that it showed benefit in the primary endpoint and also across secondary endpoints.

Next, Dr. Simon Turner will present the safety findings. You will see that the safety of olaparib and abiraterone was consistent with their established safety profiles and was manageable and tolerable. Then Dr. George will provide his clinical perspective on the favorable benefit-risk in BRCAm and non-BRCAm patients and his view on how the combination will be a very important option for

first-line mCRPC patients. And finally, I will summarize the totality of evidence in support of an all-comer indication. The following subject matter experts will be available to answer questions, and with that, I will pass it over to Dr. Shore.

Applicant Presentation - Neal Shore

DR. SHORE: Good morning. Thank you, Dr. Massacesi.

I am Neal Shore. I'm the chief medical officer of Urology and Surgical Oncology for GenesisCare in the U.S. GenesisCare has over 6,000 healthcare providers focusing on cancer care with centers in the U.S., Spain, Australia, and the UK. I also serve as the medical director of Carolina Urologic Research Center. I am a paid consultant to the sponsor, and I have no financial interest in the outcome of this meeting.

I will now present background information, including my research on advanced prostate cancer, a therapeutic area where we have experienced limited progress since the approval of novel hormonal agents nearly 10 years ago. Fortunately,

most patients with prostate cancer are diagnosed with localized disease, which can be effectively treated and cured with surgery or radiation interventions. That said, metastatic disease has a markedly different outcome. The 5-year survival rate for metastatic prostate cancer is only 30 percent, with most patients living only 2-to-3 years, asymptomatic or asymptomatic, which illustrates why prostate cancer is the second leading cause of cancer mortality for men in the U.S. This is the patient population which we will focus upon today.

In the U.S., the majority of patients receive only one approved therapy for mCRPC for their care. In a North American real-world study of over 2500 mCRPC patients, 77 percent of patients received a first-line therapy; 38 percent received a second-line therapy; and only 16 percent received a third-line therapy. Reasons for this very disappointingly low rate of second-line therapy are listed on this slide; therefore, it is critical that we provide optimal therapies for first-line

mCRPC patients, as well as subsequent lines of therapy.

Preventing and/or delaying radiographic progression is an important clinical endpoint, as stated by Dr. Weinstock. It's important in assessing oncologic treatments and is very relevant to patients and their caregivers. By offering disease stabilization and preventing clinical progression, hallmarks of the benefit for delaying rPFS, patients will have an enhanced opportunity for additional mCRPC therapies.

While rPFS is not an established surrogate for overall survival, it is strongly associated with death from multiple prostate cancer studies and is an endpoint that directly affects patients. Over the last 25 years of providing prostate cancer care, I always discuss the potential benefits of delaying progression with my patients, and these include delaying the time to new metastases; reducing the need for palliative radiation for painful bone lesions; reducing the complications of visceral metastases; and delaying the time to

initiate taxane-based chemotherapy, which is associated with neuropathy and febrile neutropenia, and of course quality of life concerns. Appreciating the unique goals for each patient is essential to the patient-physician shared decision-making process, the importance of choice.

This slide highlights the final stages of the prostate cancer disease continuum. Novel hormonal agents such as abiraterone and enzalutamide are the most commonly used first-line mCRPC treatment options. Despite the availability of numerous approved second-line mCRPC and beyond therapies, outcomes remain poor. Indeed, the overall survival in clinical trials ranges between 2-to-3 years.

Notably, real-world data from Flatiron suggest that the median overall survival within the community setting is even worse, highlighting the significant unmet need for mCRPC patients. As you will hear today, PROpel has now reported a 42-month median overall survival. This is the longest survival seen to date in first-line mCRPC.

Now, testing for alterations in the homologous repair pathway is very important to support patient-physician decision making for monotherapy PARP inhibitor use, which has been my practice since 2016. Genetic testing rates have increased since the approval of PARP inhibitor monotherapy in 2020, yet still remain underutilized in real-world practice. Less than 50 percent of academic centers are routinely performing HRR testing, and in community practices, this declines to less than 30 percent.

Multiple testing challenges exist. First, germline testing will only detect 50 percent or less of BRCA alterations in mCRPC, as the remainder are detected through somatic testing. Second, although tissue testing is preferred, it has a recognized failure rate of approximately 30 percent, often due to poorly preserved tissue and inadequate tumor DNA. Obtaining fresh tissue biopsies for the mCRPC patient can be difficult, as bone is often the only site of metastasis. And third, assessment of HRR alterations in people of

color is still evolving regarding accuracy of test interpretation, especially for variants of uncertain significance, as we described in our ASCO 2022 podium presentation.

The FDA has suggested that in order to consider a patient non-BRCAm, the patient should have an evaluable tissue test and a blood-based ctDNA test, and that both results must be negative for BRCA. Unfortunately, this is not practical in the real-world setting. The insistence on this approach will exacerbate disparities given geographic and sociodemographic challenges for testing access. Notably, if and when genetic testing is performed in the real world, only one genetic test is ordered. In other words, obtaining both tissue and ctDNA testing results is not the standard of care for community physicians.

In summary, metastatic castration-resistant prostate cancer is heterogeneous and lethal. Despite available treatments, outcomes remain poor. Delaying radiographic progression, specifically in the first-line setting, is a very meaningful

endpoint for patients and for our discussion and our choice of therapy. Where many of these patients will only experience one line of an approved therapy, it is essential that physicians and patients have an opportunity to choose their treatment in order to optimize their cancer care. For first-line mCRPC options, we have been somewhat stalled for nearly a decade.

Please allow me now to introduce Dr. Laurence Tom, who will review the efficacy of the PROpel trial.

Applicant Presentation - Laurence Tom

DR. TOM: Thank you, Dr. Shore, and good morning. My name is Laurence Toms. I'm the global clinical head for olaparib at AstraZeneca. I'm going to share with you key efficacy data for olaparib and abiraterone in first-line mCRPC. I will then move on to address the FDA's three efficacy issues as outlined in their briefing document.

PROpel is a pivotal, randomized, controlled, double-blind trial that enrolled 796 patients with

first-line mCRPC. Patients were randomized 1 to 1, stratified by sight of metastasis and prior docetaxel use, and treated with either abiraterone and olaparib or abiraterone and placebo. As agreed with the agency, the primary endpoint for PROpel was investigator assessed, rPFS; without PFS, by blinded independent central review, or BICR, as a sensitivity analysis. Overall survival was a key secondary endpoint.

Patients were enrolled in the study from November 2018 to March 2020. Data cutoff 1 took place in July 2021 with 394 rPFS events. The study was positive for rPFS at this first data cutoff. OS was tested hierarchically after rPFS, and the final analysis, DCO3, took place in October 2022. The power for OS at this time was estimated at 55 percent.

Key baseline and disease characteristics were well balanced between the arms, including the stratification factors: Gleason score, PSA, and baseline pain. PROpel was a positive study. It met the primary endpoint of investigator rPFS,

demonstrating a statistically significant and clinically meaningful 34 percent reduction in the risk of progression or death in the ITT population, which was an increase in 8.2 months in median rPFS. The rPFS by BICR demonstrated a 39 percent reduction in the risk of progression or death.

Overall survival was the key secondary endpoint of the study and showed a 19 percent reduction in the risk of death. The study wasn't fully powered to assess OS, though the p-value was 0.0544 and the confidence interval 0.67 to 1. The median OS in the combination arm was 42.1 months, which was an improvement of 7.4 months.

The secondary and exploratory clinical endpoints in the ITT population demonstrated a clinical benefit in the response of the tumor, both the PSA and radiological response, and the delay to subsequent clinically important events, including PSA progression, time to first subsequent treatment, and subsequent chemotherapy, and second progression.

The study included pre-planned analysis of

homologous recombination repair mutation status, and outcomes in HRR mutation subgroups were a secondary endpoint of the study. In order to maximize biomarker information, we planned analyses using both the tumor tissue test and the ctDNA test for all patients. Ninety-eight percent of patients on the study had both tests. These tests were performed after randomization and prior to the analysis of the study's primary endpoint. Both tests are validated and approved.

The tumor tissue test on the left is considered the reference standard, but has a high test failure rate across studies and is dependent on a high-quality sample. In PROpel, 67 percent of patients had the valid result from this test. The ctDNA test was used to complement the tumor tissue test. ctDNA identifies mutations in tumor DNA shed into the blood with a 92 percent success rate, and of note, PROpel performed testing in accordance with the FoundationOne ctDNA test label, which requires all patients with a negative ctDNA test to have a tissue test, if possible. Using the results

of both the tumor and ctDNA test in a combined or aggregate analysis allowed us to minimize the number of patients on the study without a biomarker status to just 2 percent of patients.

We did not pre-plan assessments of subgroups based on BRCA mutant status, though BRCA was part of the HRR mutation panel, and we conducted exploratory analyses of BRCA subgroups. BRCA mutant patients were well balanced between the two arms of the study, with 12 percent in the combination arm and 10 percent in the abiraterone arm. Within the non-BRCA subgroups, baseline disease characteristics were generally well balanced. Analyses of both rPFS and 0S in the BRCA mutant subgroup demonstrated clinically significant benefit. The hazard ratio for rPFS was 0.23, and for OS was 0.29.

Now looking at the non-BRCA mutant aggregate subgroups, rPFS in the non-BRCA mutant subgroup demonstrated clinically meaningful benefit. When assessed by investigator, the hazard ratio was 0.76, and by BICR, 0.72, which corresponds to an

increase in median PFS of 5 and 11 months, respectively. In addition to the benefits in rPFS, there was a delay to the time to first subsequent treatment shown on the left, and overall survival, on the right, had a hazard ratio of 0.91.

Within the non-BRCA mutant subgroup, approximately 90 percent of the ITT population, analysis of the predefined clinical factors demonstrates a consistent effect of olaparib plus abiraterone, and of note, patients with particularly poor prognostic factors, those with visceral disease or prior docetaxel use, derived a numerically greater benefit with the combination, and the pattern is similar in the OS subgroup analysis.

The secondary and exploratory clinical endpoints in the non-BRCA mutant subgroup demonstrates clinical benefit in the response of the tumor, both PSA and radiological response, and a delay to subsequent clinically important events, including PSA progression, time to first subsequent treatment, and chemotherapy and second progression;

and taken together, the totality of data supports a clinical benefit in the non-BRCA mutant subgroup.

I'd now like to take the opportunity to discuss some of the issues raised by FDA in their briefing document. Issue 1 relates to the heterogeneity of patients in the study and the lack of stratification by HRR or BRCA mutation status. PROpel was designed on the basis of the only randomized study available at the time, the proof-of-concept Study 8, a phase 2 study in an all-comers population.

Study 8 was a positive trial with an rRPF hazard ratio of 0.65. There was no evidence that HRR mutation status was a predictive biomarker, using either the initial or the final classification of the data from this study; and of note, there were only 7 patients with a BRCA mutation in this study. Removing these from the subgroup analyses showed a consistency with the ITT result.

So why then didn't we stratify PROpel by HRR or BRCA mutation status? Well, as I've shown,

Study 8 did not demonstrate HRR or BRCA was predictive of benefit, and there was also limited evidence at the time that BRCA was prognostic in first-line mCRPC. Instead, we decided to stratify on the known prognostic factors of site of metastasis and prior docetaxel use. Nevertheless, PROpel provides reliable estimates of treatment effect in biomarker subgroups.

BRCA or non-BRCA patients are generally balanced between the arms, and the baseline characteristics within the non-BRCA subgroup are well balanced. When accounting for any imbalance that did exist, analyses demonstrate that the estimates of treatment effect are reliable and the results of the study are therefore interpretable.

The FDA has stated that prospective stratification would have decreased the tumor tissue test failure rate. AstraZeneca does not believe this statement to be correct. The failure rate observed in PROpel is consistent with other studies requiring prospective testing in mCRPC, and as recognized by the FDA, obtaining fresh tissue

for biopsy in prostate cancer has often been practical and archival prostate biopsies or prostatectomy specimens are typically the source of tumor tissue testing.

Moving on to discuss the FDA's second key concern, biomarker status, this slide will explain the difference in BRCA subgroup classification between AstraZeneca and FDA. Patients are categorized by AstraZeneca as BRCA mutant if either the tumor tissue or the ctDNA tests are positive, and that was 85 patients; BRCA unknown if neither test has a valid test result, and that was 18 patients; and non-BRCA mutant in the remaining patients who were all negative by at least one test, and that was 693 patients, the aggregate non-BRCA subgroup, which included patients with both tests negative, 427 patients; only the tissue test negative, 40 patients; and only the ctDNA test negative, 226 patients.

This is the most complete data set to evaluate the non-BRCA mutant subgroup and includes all non-BRCA mutant patients. Using the FDA's

definition, non-BRCA mutant patients are limited to those who have a tumor tissue and ctDNA negative result, the so-called double-negative subgroup. This non-BRCA mutant definition excludes patients who are categorized as undetermined, the majority of whom had one negative test result.

The FDA non-BRCA mutant definition therefore excludes 36 percent of the study population and is inconsistent with the real world, where typically the result of only one test is available for clinical decision making. We do not believe the FDA's definition of the non-BRCA mutant subgroup is a reliable means of estimating treatment effect in a real-world, non-BRCA mutant patient population, who constitutes a much larger proportion of the ITT population in the study.

Shown here is a table from the FDA's briefing document in which the column in green represents the subgroup FDA refers to as undetermined, and next to it a column with the double-negative subgroup that FDA uses as a basis for assessing non-BRCA patients. Now, let me walk

you through the differences between these two subgroups, which together represent our aggregate analysis.

As you can see in the bottom of the green column, in the undetermined subgroup, the overall survival hazard ratio is 0.73. There is a minimal risk that the effect in this group is driven by misclassified BRCA mutant patients, as I'll show in my next slide. Thus, there is a clinically meaningful overall survival benefit that is derived in patients beyond those with a BRCA mutation.

Now turn your attention to the FDA's double-negative subgroup. In this subgroup, the OS hazard ratio is greater than 1. If it were true that the effect of this combination is driven by BRCA mutant patients only, adding known BRCA mutant patients to this subgroup should improve this hazard ratio, and we conducted the sensitivity analysis doing exactly that. We added a range of known BRCA patients to the double-negative subgroup, but this did not meaningfully improve the hazard ratio, which suggests that the

double-negative analysis has other intrinsic limitations, making it an unreliable way to generalize the treatment effect to the entire non-BRCA mutant population. Our aggregate analysis therefore remains the most complete, the most reliable, and the most relevant analysis for the estimation of treatment effect in the non-BRCA mutant population.

As you will hear from our practicing physicians, it's also the approach most consistent with clinical practice. If the combination of olaparib plus abiraterone were to be restricted to patients with a BRCA mutation, based on an assessment of the double-negative subgroup only, non-BRCA mutant patients would not have access to this combination and lose the potential for a meaningful clinical benefit.

As I said previously, the criticism of the AstraZeneca classification is that the ctDNA test alone may not identify all BRCA mutant patients, and these misclassified patients may drive clinical activity in the non-BRCA mutant subgroup. There

is, in fact, a low probability of misclassified BRCA mutant patients, approximately 3 percent in the group of patients with only a ctDNA result. Out of 226 patients with a ctDNA negative test and tissue test unknown, only approximately 6 BRCA patients could have been misclassified as non-BRCA mutant.

Multiple sensitivity analyses reclassifying and removing patients from the non-BRCA mutant analysis population to adjust for this misclassification show a minimal impact on the estimated treatment effects, and these data demonstrate that the treatment effect seen in the aggregate analysis of non-BRCA mutant patients is robust and not attributable to misclassified BRCA patients. I'll be happy to answer questions on our sensitivity analysis during Q&A.

Turning now to the final issue identified by FDA, overall survival benefit in non-BRCA mutant populations across studies, the FDA has suggested two sources of external validation to support an assessment of OS detriment in the non-BRCA mutant

population in PROpel. We do not agree that these provide strong supportive evidence. Firstly, in prostate cancer, the agency has cited overall survival data on the double-negative subgroup of Study 8. This analysis has limitations.

In Study 8, there were low rates of tissue testing, resulting in only 16 percent of the ITT population being in its double-negative subgroup. In this subgroup, there were just 23 patients and 18 events with high variability. Furthermore, the BRCA undetermined subgroup was 79 percent of the ITT population in Study 8, and similar to PROpel, the data demonstrated a clinical benefit in this group with a hazard ratio of 0.71. The majority of these patients had one negative BRCA test.

Secondly, in ovarian cancer, the FDA provides examples of OS detriment observed in non-BRCA mutant studies, resulting in indication restriction of other PARP inhibitors. These examples are confounded by being in a different tumor type and line of therapy, with different treatment regimens. PROpel is based on the

potential for clinical benefit outside the BRCA mutant subgroup due to the DNA repair crosstalk between olaparib and abiraterone.

In order to assess the potential for OS detriment, we reviewed the use of subsequent therapies in each arm of the study, shown here. In the non-BRCA mutant subgroup, in patients who had discontinued therapy, there is a difference of less than 8 percent, and our assessment is that this is not a clinically significant difference.

In conclusion, PROpel met its predefined primary endpoint with a 34 percent reduction in the risk of progression or death. There was a trend to improved 0S in the ITT population with a 19 percent reduction in risk of death. The aggregate non-BRCA mutant subgroup is the most complete and relevant to the real-world population, and in non-BRCA mutant patients, there was a clinically meaningful rPFS improvement of 5 months assessed by investigators and 11 by BICR, with no evidence of compromised overall survival. The totality of evidence support a meaningful clinical benefit in

this non-BRCA mutant subgroup, and with that, I'll hand it to Simon Turner to discuss safety.

Applicant Presentation - Simon Turner

DR. TURNER: Thank you, Dr. Toms.

I'm Simon Turner, patient safety, AstraZeneca. Olaparib has a well-characterized and well-tolerated safety profile, based on the experience of over 20,000 patients in clinical trials, more than 140,000 patient-years exposure, and the marketed setting over the last decade. The most commonly reported adverse reactions are generally mild to moderate and can be effectively monitored for and managed.

Abiraterone is the established standard-of-care therapy in metastatic castration-resistant prostate cancer. It has a distinct safety profile with no significant overlapping toxicities with olaparib. The safety data presented here includes the 794 patients who received either olaparib plus abiraterone or placebo plus abiraterone in the PROpel study. The median duration of survival follow-up was 3 years

in PROpel, one of the longest of any study in mCRPC. Median duration of exposure was longer for both olaparib and abiraterone in the combination arm, suggesting patients would tolerate in the therapy without progression.

Importantly, the median duration of exposure to standard-of-care abiraterone was increased by over 4 months when combined with olaparib. A higher proportion of patients in the olaparib plus abiraterone arm remained on treatment at 1, 2, and 3 years than in the placebo arm. Combining abiraterone with olaparib enables extended exposure to abiraterone without progression. This is significant because it enables patients to delay starting parenteral chemotherapies, which have adverse effects that can significantly impact quality of life such as neuropathy and alopecia.

More patients on the olaparib arm than on the placebo arm experienced a grade 3 or higher adverse event or a serious adverse event; however, the number of treatment-emergent adverse events with a fatal outcome was similar between arms.

Dose interruptions and reductions are the main strategies to effectively manage olaparib adverse events. The incidence of dose modifications of olaparib in PROpel were similar to that reported in other studies with olaparib as a monotherapy. Anemia, a well-known effect of PARP inhibition, was the most frequent adverse event requiring dose modifications or discontinuations of olaparib. Overall, the combination was well tolerated, as over 80 percent of patients were able to continue to receive olaparib until progression. This continuation rate for abiraterone was similar between arms.

Consistent with the known safety profile of olaparib built over the last decade, the most common all-grade adverse events with olaparib plus abiraterone were anemia and fatigue, as well as gastrointestinal effects such as nausea, diarrhea, constipation, decreased appetite, and vomiting. Adverse effects of abiraterone are also evident such as hypertension, arthralgia, peripheral edema, and urinary tract infections. You also see some

disease-related events such as back pain, as well as COVID-19 events, as this study was conducted at the height of the global pandemic.

Most of these adverse events were grade 1 in severity. Anemia was the most common grade 3 or 4 adverse event. Anemia is the most common adverse effect of olaparib, but it predominantly occurs early in treatment and can be effectively monitored for and managed. This plot shows the number of new onset adverse events of anemia in the olaparib plus abiraterone arm every month.

Anemia is managed with dose interruptions or dose reductions and standard supportive care methods. These interventions mean that relatively few new onset events occur after the first 3 months of treatment. Gastrointestinal effects such as nausea, vomiting, and diarrhea follow a similar pattern with early onset and relatively few events occurring after the first 3 months of treatment. Overall, the principal adverse effects for olaparib are both predictable and manageable, and the data in PROpel was consistent with the known safety

profile of olaparib.

Adding olaparib to abiraterone had no clinically meaningful impact on both overall health-related quality of life or any of the measured subscores. This plot shows mean FACT-P total score values by treatment arm, which were assessed every 4 weeks during the first year of treatment, and then every 8 weeks until treatment discontinuation. FACT-P total score ranges from 0 to 156, with higher values indicating better overall health-related quality of life. Quality-of-life scores were similar in both arms throughout the study.

The majority of patients in both treatment arms reported that they were either not bothered at all by side effects or only bothered a little bit. The FACT-P item GP5 measured how bothered patients were by the side effects of treatment, from not at all to bothered very much. This plot shows the first 6 months of the PROpel study, which is when we'd expect most impact of the adverse effects of olaparib. The small difference in favor of the

placebo arm and the number of patients reporting that they were bothered a little bit by side effects is not surprising, given the higher incidence of adverse events in the combination arm. Importantly, very few patients reported there were bothered either quite a bit or very much by side effects. This is consistent with the majority of adverse events being grade 1 in severity.

The most common adverse event with a fatal outcome on the olaparib plus abiraterone arm was COVID-19. Twelve patients died from COVID-19 on the olaparib plus abiraterone arm, compared with three on the placebo arm. This imbalance reflects a high proportion of patients with multiple risk factors for mortality from COVID in the olaparib plus abiraterone arm. All of the COVID deaths occurred during the global peak of COVID mortality, between June 2020 and March 2022. Less than a third of patients in both arms received a COVID vaccination during the study. None of the adverse events with a fatal outcome in the olaparib plus abiraterone arm were considered related to study

therapy by the investigator.

The PROpel study was designed to assess safety and efficacy in an unselected population, recognizing the differential effects of olaparib on efficacy data in BRCA mutant versus non-BRCA mutant patients. It' important to look at the safety data in the non-BRCA mutant subgroup. The overall safety analysis set data is on the left; the non-BRCA mutant aggregate subgroup is shown on the right. There are some small numerical differences in the instances of individual all grade on grade 3 or higher adverse events, but, overall, the safety profile of olaparib plus abiraterone in the non-BRCA mutant subgroup was very consistent with the overall safety analysis set , and this is what we'd expect since no differences in the safety profile by biomarker status has been reported in other olaparib studies or indeed with other PARP inhibitors.

With the exception of COVID-19, the number of adverse events with a fatal outcome was balanced between arms in the non-BRCA mutant subgroup.

Overall, there was no evidence of substantive toxicity from the combination in the non-BRCA mutant subgroup that could have adversely affected patients' ability to derive benefit from the combination.

In conclusion, olaparib and abiraterone have well-characterized, tolerable, and manageable safety profiles. The safety data from the PROpel study was consistent with the known monotherapy safety profiles. The PROpel study has one of the longest durations of survival follow-up in mCRPC. Importantly, the duration of exposure to standard-of-care abiraterone was increased by combination treatment with olaparib, with no clinically meaningful impact on overall quality of life versus the control arm.

Adverse effects of olaparib generally occur early in treatment, and there was no evidence of substantive toxicity from the combination in terms of its effect on the ability of patients to receive standard-of-care therapy, subsequent therapies, or on fatal adverse events that could have adversely

affected the overall survival results. Overall, the safety profile of olaparib plus abiraterone supports a positive benefit-risk for this combination in mCRPC.

Now, I'd like to invite Dr. George to the podium to discuss his clinical perspective.

Applicant Presentation - Daniel George

DR. GEORGE: Thank you, Dr. Turner.

My name is Dan George. I'm a professor of medicine and surgery and a practicing genitourinary medical oncologist at the Duke Cancer Institute. I am a paid consultant to the sponsor, but I have no financial interest in the outcome of this meeting. I'd like to discuss my clinical perspectives on the use of this combination for patients with mCRPC.

There are now three independent studies that demonstrate clinical benefit with the addition of PARP inhibition to novel hormonal agents in unselected mCRPC patients. In addition to Study 8 and PROpel, TALAPRO-2, a phase 3 trial of enzalutamide with or without talazoparib in mCRPC patients, has also demonstrated a statistically

significant rPFS benefit in a biomarker unselected patient population. The top line results were reported at this year's GU ASCO's conference. I mentioned the TALAPRO-2 study results only to highlight the consistency of the rPFS benefit in unselected patients across multiple studies.

The PROpel trial has demonstrated a statistically significant and clinically meaningful improvement in median rPFS of 8.2 months with a hazard ratio of 0.66 by investigator assessment. Overall survival showed a strong trend towards benefit with a median of 42.1 months for the combination, exceeding all reported and published phase 3 trial results, and thus now sets a new reference standard for treatment outcomes.

For context, despite access to more recently approved agents for mCRPC patients, shown by Dr. Shore, the median survival seen in the abiraterone control arm of PROpel was identical to that reported in the abiraterone arm of COUGAR-302 [ph], highlighting the lack of progress over nearly ten years and the importance of

improving our first-line treatment options for these patients.

Now, I routinely test for genetic alterations in mCRPC, including HRR mutations, and this status informs my practice in recommending what treatment options patients should consider. However, the reality is that HRR status can influence our recommendations, but it's challenging to implement. It rarely involves more than one assay, and it's imperfect. Recent data suggests that the majority of mCRPC patients still may not have known BRCA or HRR status due to uninformed test results or a lack of testing.

In practice, there are fundamentally three different patient scenarios we could face surrounding the clinical option of olaparib plus abiraterone, as shown here: first, patients who could have a positive BRCA test result; second, patients who could have a negative BRCA test result; or it could be patients whose BRCA status is unknown. For my patients with an identified BRCA mutation, the benefit of combining abiraterone

and olaparib is unequivocal. Unless there's a compelling medical reason not to, we should be offering this combination to all of these patients.

For patients identified as non-BRCA, the clinical benefit for olaparib and abiraterone is more modest, but it's still meaningful. The combination demonstrates the best chance to improve upon our first-line treatment results. Now, some clinicians may not view an improvement in the median rPFS of 5-to-11 months over the best standard of care as meaningful, but in my clinical experience, many of my patients at this stage of disease will be motivated by this degree of benefit. In addition, although not powered in the subset analysis, the overall survival curve trends in the positive direction, and it may actually improve over time, based on the late split in the rPFS curves that we see.

Now why would a patient choose this combination? Because as Dr. Shore mentioned, our patients want to maintain their current lifestyle. They want to delay clinical deterioration and

decrease the need for palliative radiation or opioids, and they want to delay the time to chemotherapy, which will alter their lifestyle, if they can even tolerate it. In terms of toxicity, it's important to recognize that over 80 percent of patients tolerated olaparib long term with what is best characterized from the patient-reported data as little to no bother. That's a much better outlook than any of the treatment options that will follow this.

Finally, there are the patients with an undetermined BRCA status. Now, the FDA has defined patients with undetermined status to include patients with either one negative test result or no test result, which is shown in the green box in the left table. Looking at this subgroup, there's a clear benefit with the combination. The rPFS signal is positive with a similar effect size to the ITT analysis with 95 percent confidence indices that do not cross 1 and a strong trend in overall survival benefit.

That's hardly what you'd expect if you

believe that all the benefit in the ITT population is driven by the BRCA mutant subgroup, and while any retrospective subgroup analysis should be interpreted with caution, if we're going to evaluate the double-negative BRCA subgroup, it's important to put that cohort into context with the patients that we arbitrarily excluded. In reality, this, quote, "undetermined" BRCA subgroup, particularly those with one negative blood test, represents the vast majority of the mCRPC patients that I currently treat in my practice. And most importantly, if you restrict the PROpel approval to the BRCA mutant subgroup, this large proportion of non-BRCA mutant patients in the real world will be denied the option to receive this combination and any hope of additional clinical benefit.

In summary, there's no doubt that patients with a BRCA mutation derive the greatest benefit from the combination, an approach with more than over 70 percent improvement in overall survival. Despite a smaller clinical benefit, patients most commonly report little to no bother with this

combination, and therefore many patients without an underlying BRCA mutation or do not have known BRCA status will view this benefit-risk profile as favorable. This is not necessarily a treatment for all mCRPC patients, but improving rPFS in the first-line mCRPC setting is a welcomed goal for many of our real-world patients. Based on the PROpel data, patients and physicians should be allowed to decide whether to combine olaparib with abiraterone for treatment of their mCRPC.

I'd like to now hand the podium back to Dr. Cristian Massacesi for final comments.

Applicant Presentation - Cristian Massacesi

DR. MASSACESI: Now allow me to summarize the key data response to FDA's three discussion points. First, PROpel enrolled a real-world, first-line mCRPC population. The all-comer approach is supported by mechanistic and nonclinical data, as well as the Study 8 results, where the HRRm subgroup analysis was not predictive, nor prognostic. Ultimately, despite no stratifying for biomarker status, the biomarker

subgroups were balanced between treatment arms.

Second, we showed that the aggregate analysis for non-BRCAm is rigorous and provides the most complete data set. It has a low risk of misclassification and is most consistent with clinical practice, as you heard from Dr. Shore and Dr. George right now.

Thirdly, and most importantly, the data gives us confidence that there is no detriment in OS and in non-BRCAm subgroup. In PROpel, primary and secondary endpoints confirm a meaningful clinical benefit in this population. As Dr. Toms showed, we cannot conclude that there is an OS detriment in Study 8 in this population, based on a very small sample size and very few events in the analysis presented by FDA.

Lastly, as FDA members stated in a recent Journal of Clinical Oncology publication, to observe a detriment in OS, we should assume an impact on safety or subsequent treatment. In PROpel, we have seen no increase in treatment-related deaths and no impact on ability

to receive subsequent therapies in non-BRCAm patients. Therefore, the totality of evidence does not support a detriment in OS in the non-BRCAm subgroups.

In summary, PROpel resulted in a positive benefit-risk for olaparib plus abiraterone in all-comers and in non-BRCAm mCRPC patients. This is demonstrated by a clinically meaningful improvement in median rPFS in both ITT and non-BRCAm subgroups, a trend towards improvement in overall survival in ITT and no evidence of OS detriment in non-BRCAm subgroup; a predictable and manageable safety profile for the combination of olaparib and abiraterone that allowed actually increased exposure to standard-of-care abiraterone; and no clinically meaningful impact on quality of life.

PROpel is a positive study that met its primary objective in an all-comer mCRPC population. As discussed by Dr. George, the greatest benefit is seen in BRCAm patients. The data also show that the benefit-risk profile in non-BRCAm patients

remains positive. We recognize the important role of biomarker testing in prostate cancer. We therefore support testing and consider that a complementary diagnostic is useful to inform physicians and patients of the expected benefit-risk for the BRCAm and non-BRCAm subgroups.

In conclusion, the totality of evidence that we presented today support the proposed indication. Lynparza in combination with abiraterone and prednisone, or prednisolone, is indicated for the treatment of adult patients with metastatic castration-resistant prostate cancer. Thank you, and we look forward to your questions.

DR. GARCIA: Thank you very much to the AstraZeneca team and its presenters.

We will now proceed with the FDA presentation from Dr. Jaleh Fallah.

Dr. Fallah?

FDA Presentation - Jaleh Fallah

DR. FALLAH: Thanks, Dr. Garcia.

Good afternoon. I am Jaleh Fallah, a medical oncologist at the FDA. This supplemental

new drug application for olaparib was submitted by AstraZeneca, which I will hereby refer to as the applicant. This slide lists the members of the FDA review team, and my presentation reflects our collective input.

The applicant's proposed indication for olaparib, in combination with abiraterone, and prednisone or prednisolone, is for the treatment of adult patients with metastatic castration-resistant prostate cancer, briefly called mCRPC for the rest of this presentation. As Dr. Weinstock mentioned in her presentation, we would like to ask the following question from ODAC.

As FDA reviews the proposed indication for olaparib in combination with abiraterone for initial treatment of mCRPC, should the indication be restricted to patients whose tumors have a BRCA mutation? If you feel the combination should not be approved at all, please abstain from voting and explain your thinking regarding approvability during the post-voting discussion period. In the following presentation, I'm going to explain why we

are asking this question from the committee.

Homologous recombination repair, or HRR, is an essential pathway for DNA repair. Several genes are directly or indirectly involved in HRR pathways such as BRCA1, BRCA2, and ATM. Mechanistic and clinical data support that mutations in BRCA, and potentially other HRR genes, may sensitize tumor cells to PARP inhibition, and that BRCA mutation status in particular is a strong predictive biomarker for PARP inhibitor efficacy. In this presentation, HRRm refers to mutation in genes involved in HRR pathway and BRCAm refers to mutation in BRCA genes.

The applicant initially conducted a small randomized phase 2 clinical trial called Study 8, which assessed the efficacy and safety for adding olaparib to abiraterone in 142 patients with mCRPC who had disease progression on prior docetaxel. This study was designed in 2013 when less was known about the strength of BRCA as a predictive biomarker and randomization was not stratified by BRCA or HRR mutation status. The primary endpoint

was radiographic progression-free survival, or rPFS, by investigator assessment.

In 2018, the applicant presented the top-line results of Study 8 to the FDA, proposing to submit an application for accelerated approval in a unselected population. The study met its primary endpoint in the ITT population, showing statistically significant improvement in investigator-assessed rPFS when adding olaparib to abiraterone.

The applicant submitted an exploratory subgroup analysis by HRR mutation status, and based on the results shown in the table, the applicant concluded that there is benefit from olaparib, regardless of the presence of a sensitizing mutation in the tumor. However, the HRR mutation status of the tumor was unknown for more than half of the patients, and overall survival for these patients was not provided at that time. Additionally, rPFS assessment by blinded independent central review was not available yet.

In May 2018, in a meeting with the

applicant, FDA discouraged submission of an application for accelerated approval since Study 8 was a small exploratory study with low confidence in the results, and that the majority of patients had unknown HRR mutation status, which might lead to imbalances between the two arms.

The applicant agreed to not pursue an accelerated approval based on Study 8 alone and acknowledged the need to assess the potential impact of HRR mutation on efficacy. At that time, the applicant also informed the FDA of their plan to conduct a phase 3 clinical trial called PROpel to confirm the results of Study 8.

To support the proposed indication, the applicant submitted the results of PROpel, a double-blinded, randomized, placebo-controlled clinical trial, which randomized 796 patients with mCRPC in 1-to-1 ratio to receive abiraterone in combination with olaparib or placebo. Randomization was stratified by site of metastases and prior treatment with taxanes in a hormone-sensitive setting. The primary endpoint of

PROpel was rPFS by investigator assessment with a plan to assess rPFS by BICR as a sensitivity analysis. The key secondary endpoint was overall survival.

Despite the applicant's acknowledgement of the importance of evaluating potential impact of sensitizing mutations on efficacy, there was inadequate determination of tumor mutation status in PROpel. The study was not stratified by tumor mutation status for BRCA or other HRR genes, and there was no prespecified alpha-controlled analysis by tumor mutation status.

Before I present the study results, I want to note that this trial design would not be appropriate today, given the additional information we currently have about the efficacy and safety of PARP inhibitors in patients without BRCA mutations. BRCA mutation status should be prospectively, determined and the efficacy results should be analyzed separately for biomarker positive and negative populations.

PROpel met its primary endpoint of rPFS by

investigator assessment. The hazard ratio was 0.66 with 8 months improvement in median rPFS when adding olaparib to abiraterone compared to placebo and abiraterone. Although PROpel did not statistically meet the secondary endpoint of overall survival, the hazard ratio for OS was 0.81, which suggests that there was no OS detriment.

For this type of add-on trial design, FDA generally considers a large improvement in rPFS with supportive OS results and an acceptable toxicity profile to support a favorable benefit-risk assessment in a homogeneous patient population with mCRPC. However, PROpel enrolled a heterogeneous population with respect to BRCA status and sensitivity to PARP inhibitors, which raises the question of whether the results in the ITT population demonstrates a favorable benefit-risk profile for olaparib, regardless of the tumor mutation status or not.

For the rest of the presentation, I will go through the key efficacy and safety issues of the application, the role of subgroup analysis in

regulatory decision making, and finish with the ODAC voting question. The first efficacy issue is that while BRCA mutation is a known strong predictive biomarker of response to PARP inhibitors, PROpel enrolled a heterogeneous population unstratified by BRCA status.

Clinical trials of PARP inhibitors in patients with prostate cancer have demonstrated a strong correlation between the presence of tumor BRCAm and efficacy, regardless of administration of monotherapy or in combination with an androgen pathway inhibitor. This table shows the public rPFS results of other trials in prostate cancer, including PROfound, TRITON-3, MAGNITUDE, and TALAPRO-2 by BRCAm or HRRm status. The hazard ratio of rPFS for the subgroup with BRCAm is much smaller than that in other subgroups, which suggests efficacy was primarily attributable to patients with BRCA mutation.

I would also like to note that other trials in this setting were designed with prospective determination of and stratification by HRRm and/or

BRCAm status, and some have had formal analysis of the cohorts without a mutation. MAGNITUDE, which assessed another PARP inhibitor, niraparib, in combination with abiraterone, is a good example of this, as it both enrolled a separate non-HRR cohort and stratified by BRCAm status within the HRRm cohort.

It is noteworthy that in the MAGNITUDE trial, the non-HRRm cohort was stopped for futility per publicly available sources. Overall, the efficacy of PARP inhibitors across trials in prostate cancer appears to be primarily attributable to the effects seen in patients with BRCAm subgroups with, at best, modest efficacy for other patients.

The strong correlation between the presence of BRCA mutation and sensitivity to PARP inhibitors and lack of benefits in subgroups without BRCA mutations has been demonstrated across other solid tumors such as ovarian cancer. This table shows the results of NOVA and ARIEL3, two trials in patients with recurrent metastatic ovarian cancer,

where PARP inhibitors were used for maintenance treatments. In both trials, the PFS benefit was more remarkable in the BRCAm subgroups. For non-BRCAm, the hazard ratio for PFS was around 0.5 and the hazard ratios for final overall survival analysis were 1.06 and 1.08; and due to concern for OS detriment and potential harm from treatment with PARP inhibitors in non-BRCA subgroups, both indications were subsequently restricted to patients with BRCA-mutated tumors.

The second efficacy issue is inadequate determination of tumor BRCAm status in PROpel. In PROpel, BRCA mutation status was assessed retrospectively by the FoundationOne assay, which uses tumor tissue, and the FoundationOne Liquid assay, which uses circulating tumor DNA obtained from patients' plasma. Both tests were previously approved for selection of patients with HRR or BRCA mutation for treatment with olaparib or rucaparib in more advanced settings.

This table shows the positive percent agreement, or PPA, and negative percent agreement,

or NPA, of ctDNA BRCA tests across clinical trials using the tumor tissue test as reference. The PPA across these trials is relatively low, indicating that there is a potential for false negative results and the negative ctDNA test result is not sufficient to rule out the presence of a BRCA mutation. On the other hand, the high NPA of the ctDNA test indicates that the likelihood of false positive is low, and having a positive result is sufficient to consider patients' tumor as having a BRCA mutation. FDA labeling for the FoundationOne assays states that a negative result does not rule out the presence of a mutation in the patient's tumor and that a negative ctDNA test result should be reflex to routine biopsy and tumor tissue test.

This table shows the concordance for the ctDNA and tumor tissue test in PROpel and demonstrates the likelihood of positive results in the other tests when one test is negative.

Two percent of the ITT population had a negative tumor tissue test but a positive ctDNA test result, and 2 percent had a negative ctDNA and a positive

tumor tissue test result.

We note that over a third of patients in PROpel did not have non-BRCA status confirmed by tissue testing due to various tissue and assay issues; however, had the applicant required prospective assessment of BRCA status, confirmation of BRCA status may have been improved; for example, by re-biopsy rather than relying on an archived prostate biopsy sample. Just one negative ctDNA or tumor tissue test is not sufficient to rule out the presence of BRCA mutation. FDA defines three subgroups, based on the likelihood of having a tumor BRCA mutation.

One, BRCAm in the green row is the subgroup of 11 percent of the ITT who are patients with one or two positive BRCA tests. Because of the high NPA of both tests, there is high certainty that these patients have a tumor BRCA mutation.

Two, non-BRCAm in the red row is a subgroup of 54 percent, over half of the ITT, who are patients with 2 negative BRCA tests. The non-BRCAm subgroup is defined with confirmed negative results

mainly due to the observed low PPA of ctDNA tests. In this non-BRCAm subgroup, there is high certainty that these patients do not have a tumor BRCA mutation.

Three, undetermined BRCAm status in yellow is a subgroup of 35 percent of patients in the ITT who had unknown status on one test and negative or unknown results on the other tests. Considering the relatively low PPA for FoundationOne assays, which is not sufficient to rule out the presence of mutation, it is likely that some patients in this subgroup actually had a BRCA mutation.

The next efficacy issue is consistent results across trials, raising concern for harm and potential OS detriment from olaparib in patients without tumor BRCA mutations. This table shows the subgroup analysis of rPFS by investigator assessment and OS by BRCA status in PROpel. The hazard ratios for rPFS and OS for BRCAm are 0.24 and 0.3, much smaller than hazard ratios for the other two subgroups, indicating that results of the ITT population are mainly attributed to the

treatment effect in BRCA-containing subgroups.

On the other hand, the upper bound of 95 percent confidence interval for rPFS in the non-BRCAm subgroup crosses 1, and the hazard ratio for OS in this subgroup is above 1, indicating marginal, if any, improvement in rPFS and concern for OS detriment in the non-BRCA subgroup, which represents the majority of the patients in PROpel and in the real world.

Here are the Kaplan-Meier curves for rPFS and OS for the three subgroups. The upper panel presents the Kaplan-Meier curves for rPFS, where olaparib is red and placebo is blue, and further illustrates the noticeable difference in treatment effect of olaparib in the three subgroups. The left figure is for BRCAm where the two curves are clearly separated, and the right figure is for non-BRCAm, where the difference of the two curves is marginal.

The Kaplan-Meier curves for overall survival show a consistent pattern, suggesting a strong association between presence of BRCA mutation and

benefit from olaparib. Notably, the bottom-right figure is for non-BRCAm, and it shows the blue line is above the red line for the first 20 months, indicating a higher death rate in the olaparib arm compared to placebo for about 20 months, which could be the major reason for a hazard ratio over 1 in this subgroup. These Kaplan-Meier curves suggest that there is potentially no benefit and concern for harm in patients with non-BRCAm status.

With exploratory post hoc subgroup analysis, there does exist the potential for imbalance in baseline covariates, so the FDA examined the prognostic factor balance between two arms for the three subgroups by BRCAm. Despite lack of stratification, baseline prognostic factors were well balanced between treatment arms in the undetermined in the non-BRCA subgroups due to the large sample sizes. The individual prognostic factors examination did not identify any notable imbalance. Furthermore, a validated prognostic risk model for mCRPC, which combines 8 prognostic factors, was employed to assess overall balance,

and the results showed balanced risk score.

On the other hand, there is an imbalance of prognostic factors in the BRCAm subgroup, which is in favor of the olaparib arm. This is not surprising due to the small sample size of this subgroup. Nevertheless, adjustment methods for imbalance had little impact on the observed strong treatment effect in the BRCAm subgroup. Overall, after adjustment for baseline prognostic factors in the three BRCA-based subgroups in PROpel, there were no overall changes in the conclusions that the efficacy results in the ITT population were primarily attributed to efficacy in the BRCAm subgroups.

In PROpel, we see internal consistency between primary and secondary endpoints, showing a consistent pattern for differential treatment effect from olaparib by BRCAm mutation status. The hazard ratios of rPFS by BICR for the three subgroups are 0.19, 0.59, and 0.82, respectively, showing an even more prominent difference in magnitude of benefit between these subgroups,

further suggesting that the benefits in ITT population is primarily attributed to the treatment effect in patients with BRCAm disease. Additionally, the rPFS difference in the known BRCA subgroup by BICR assessment is only 3 months. This is equal to the imaging interval for rPFS assessment in PROpel, which indicates that the actual rPFS difference could be even smaller than 3 months.

Assessment of the confirmed objective response rate in patients with evaluable disease show a noticeable difference in the treatment effect from olaparib between the subgroups. We observed that in non-BRCA subgroups, objective response rates are similar between two arms for this add-on design, further indicating lack of benefit by adding olaparib for the non-BRCA subgroups.

Combining all patients without a test demonstrating BRCA mutations -- that is those in the undetermined BRCAm and non-BRCAm subgroups -- yields a subgroup representing

89 percent of the enrolled population, shown here as the orange column. This is a very similar population to the non-BRCA subgroup defined by the applicant, but also includes 18 patients who had unknown results for both tests.

While these results demonstrate activity of olaparib in this subgroup, an important consideration for the committee is whether the 5-month improvement in investigator-assessed rPFS is clinically meaningful, given the add-on design, long duration of exposure to the toxicities of olaparib for over a year and a half, and lack of OS improvement. In addition, this subgroup potentially includes a small proportion of patients who had an unidentified BRCA mutation, and it is not clear to what extent the 5-month improvement in rPFS may be attributed to efficacy in these patients.

While the median rPFS improvement by BICR in this subgroup was 11 months, the FDA considers this 11-month improvement to be overestimated and unstable for the following reasons. As shown in

the Kaplan-Meier curve of rPFS by BICR in this subgroup, on the right side, the median was estimated towards the tail of the Kaplan-Meier curve for the olaparib arm, which is in red, where there were very few events, which caused an overestimation in the median rPFS difference between treatment arms.

In the subsequent analysis of rPFS at data cutoff 2, there was an 8-month difference between the arms by BICR assessment, which shows that the BICR measurement of rPFS at data cutoff 1 was overestimated. Additionally, as previously, discussed, the median rPFS Improvement by BICR in the non-BRCA subgroup was only 3 months; therefore the observed 11 months for all others, even if considered reliable, was largely attributed to the undetermined BRCAm subgroup, which include patients with unidentified BRCA mutations. And lastly, rPFS by investigator assessment was the primary endpoint in PROpel, and the second review of BICR results should be considered only as supportive.

Let's now revisit the results from Study 8,

which, as discussed earlier, also assessed the combination of abiraterone plus olaparib or placebo in an unselected population with mCRPC. Recall Study 8 showed a significant improvement in investigator-assessed rPFS. At the time of submission of the PROpel results, the applicant also submitted updated Study 8 results, including rPFS by BICR assessments and overall survival by HRR mutation status of the tumor.

However, the analysis of rPFS by BICR assessment shows that there was no statistically significant difference between the arms in the ITT population, with a hazard ratio of 0.95. In addition, when considering the same three groups of BRCA status that FDA assessed in PROpel, 16 percent of patients in Study 8 had non-BRCAm status. In this subgroup, the observed hazard ratios for rPFS by BICR assessment and overall survival were about 1, which is concerning for potential harm from olaparib in patients without the BRCA mutation in their tumor.

Although interpretation of Study 8 results

is limited by the small number of patients, the efficacy results in the subgroup with non-BRCAm and undetermined status are consistent with the efficacy results for these patients in PROpel. When findings from two separate trials are consistent, they are less likely to be merely due to chance and further raises the concern for lack of efficacy and potential harm from olaparib in patients without the BRCA-mutated tumor.

The key safety issue is that adding olaparib to abiraterone increases toxicity and symptom burden, which may be unacceptable for an add-on to an effective and well-tolerated therapy, and patients without tumor BRCA mutation may become exposed to other toxicities of olaparib for over a year before lack of efficacy from the add-on therapy become apparent.

While the overall safety profile of abiraterone and olaparib in the PROpel study were consistent with known toxicities of PARP inhibitors and androgen receptor pathway inhibitors, the combination therapy arm of PROpel was considerably

more toxic than the abiraterone and placebo arm, with 30 percent more reports of high-grade adverse reactions, 67 percent more reports of nausea and vomiting, and more than double the rates of myelosuppression, blood transfusion, and thromboembolic events.

Of note, approximately 1-out-of-5 patients in the olaparib arm received at least one blood transfusion. The most common cause of death due to adverse reactions in both treatment arms was infection. The higher rate of bothersome symptoms, such as nausea, vomiting, diarrhea, higher need for blood transfusion, and risk of thromboembolism, can have meaningful adverse impacts on patients' lives, particularly in this early setting in mCRPC, where patients are generally minimal asymptomatic.

Patient-reported outcomes were collected in the PROpel study using the FACT-P instrument. To assess the tolerability aspects of the patient-generated data, FDA specifically focused on the descriptive results overall side effect impact item, GP5. In the literature, Saad and colleagues

previously described minimal androgen receptor pathway inhibitor side effect impact compared to placebo. In PROpel, patient-reported outcomes were included as exploratory and descriptive information, and the adequate completion rates allowed for analysis and interpretation of these results.

Although a formal comparative tolerability endpoint was not included in PROpel, FDA noted a higher proportion of patients in the PROpel arm who reported side effect bother compared to placebo. That being said, in both arms, there were few patients who reported severe bother. Overall, these GP5 results support the clinician-reported findings as mentioned on the previous slide of tolerability concerns when olaparib is added to abiraterone.

The applicant proposes a biomarker unselected indication for olaparib in combination with abiraterone in first-line mCRPC. As mentioned earlier, the majority of patients in PROpel and in the real-world setting do not have BRCA mutation in

their tumor, and the exploratory subgroup analysis from two trials of this regimen showed a marginal rPFS improvement and potential for OS detriment in the subgroup with two negative BRCA tests.

Approval of olaparib in an unselected population with mCRPC exposes a large number of patients to the toxicities of olaparib with likely minimal chance of benefit from add-on therapy for a duration of longer than one year. This unnecessary exposure to olaparib in the absence of benefit is associated with a higher risk of adverse events, greater symptom burden, and potential OS detriment as a result of treatment with olaparib, and we reiterate, these toxicities would be experienced by a patient population that otherwise is generally minimal asymptomatic and may be treated with a well-tolerated monotherapy of abiraterone.

The subgroup of patients with unconfirmed BRCAm status is an artifact resulted from inadequate determination of tumor BRCA mutation status in PROpel. This subgroup is a heterogeneous mixture of a very small number of patients with

unselected BRCA mutation and the much larger population accounting for more than 90 percent of this subgroup whose tumors are truly negative for BRCA mutation. Given the potential toxicity and worsened survival demonstrated in patients with confirmed non-BRCA status, we are concerned that blindly adding olaparib to abiraterone without confirming the BRCA mutation status may cause harm to the great majority of this patient population that is truly negative for BRCA; and while if this was a monotherapy and lack of efficacy may be detected early and the drug stopped, the addition of olaparib to an effective partner means that patients without the likelihood of benefit may be subjected to the toxicities of olaparib for over a year.

Now, I will briefly talk about the role of subgroup analysis in regulatory decision making. The International Council for Harmonisation, or ICH, guideline for planning and design of multiregional clinical trials has emphasized the importance of the assessment of consistency of

treatment effects across the study subgroups to inform the regulatory decision making, and recommended evaluating the credibility of subgroup findings by several factors, including the biological plausibility; internal consistency between primary and secondary endpoints of a trial; external consistency across clinical trials; the strength of evidence; clinical relevance; and statistical uncertainty.

Although subgroup analyses are generally considered exploratory and cannot be used to salvage a failed trial, it can be used to narrow the indication when there are safety or efficacy concerns and strong biologic rationale, particularly when there is also external consistency across trials. According to the FDA labeling guidance for drugs and biological products, if a study demonstrates benefit only in a biomarker-based subgroup, the FDA may determine that the evidence supports an indication in a narrower population than was enrolled overall.

This table provides some examples of that.

FDA had restricted an indication based on lack of efficacy, added toxicity, and concern for OS detriment in a subgroup. These include limitations of use for permetrexed to patients with non-squamous non-small cell lung cancer; for the eGFR inhibitors cetuximab and panitumumab to patients with KRAS wild-type metastatic colorectal cancer; restricting the indication for olaparib and bevacizumab to patients with ovarian cancer with homologous recombination deficiency as defined by a BRCA mutation or a high tumor genomic instability score; for adjuvant pembrolizumab to patients who had previously been treated with platinum-based chemotherapy; and elacestrant to patients with ESR1-mutated breast cancer

The FDA conclusions are as follows:

1) Despite the suboptimal design of PROpel to assess the efficacy by mutation status, the rPFS improvement in all-comers is attributed to efficacy in the BRCAm subgroup.

2) For patients who are negative for tumor BRCA mutations by two essays, we are concerned that

PROpel demonstrated a lack of efficacy and a potential overall survival detriment. This population comprises over half of the ITT population. Even if considering the 89 percent of the population without the demonstrated tumor BRCA mutation, the rPFS improvement in this setting is of dubious clinical meaningfulness, given the add-on design and exposure to additional toxicity for the large proportion of patients with true underlying lack of tumor BRCA mutation who are unlikely to benefit from therapy.

3) There was minimal impact, and a lack of stratification and results were consistent for the three BRCA subgroups after adjusting for baseline characteristics based on prognostic model for mCRPC.

4) There is internal consistency between primary and secondary endpoints, demonstrating modest efficacy from adding olaparib in the non-BRCA subgroup.

5) There is external consistency across trials showing modest efficacy and potential harm

from PARP inhibitors in patients without BRCA mutation. These trials include Study 8, which was another study of olaparib plus abiraterone, studies of other PARP inhibitors in prostate cancer, and studies in patients with other cancers, including advanced ovarian cancer. BRCA mutation status consistently appears to be a strong predictive biomarker for PARP inhibitor efficacy.

6) Due to the addition of olaparib to abiraterone, patients with non-BRCA tumors are at risk of exposure to toxicities of olaparib for longer than one year without likelihood of benefit. Ultimately, we are concerned that olaparib may represent a toxic placebo with potential for harm in patients without tumor BRCA mutation.

We would like to ask the following question from ODAC. As FDA reviews the proposed indication for olaparib in combination with abiraterone for initial treatment of mCRPC, should the indication be restricted to patients whose tumors have a BRCA mutation? If you feel the combination should not be approved at all, please abstain from voting and

explain your thinking regarding approvability during the post-voting discussion period.

That concludes my presentation, and now I will turn it over to Chair, Dr. Garcia. Thank you.

Clarifying Questions to Presenters

DR. GARCIA: Thank you, Dr. Fallah.

We will now take clarifying questions for the presenters, AstraZeneca Pharmaceuticals, LP and the FDA. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon again after you have asked your question. 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 the end of your follow-up question with, "That is all for my questions," so we can move on with the next panel member

I have a comment and a question, so maybe I'll just make my comment and ask the question, and then we can move on. I see there are some hands already up.

I cannot ignore the fact that I'm a GU medical oncologist and also take care of men with prostate cancer, so I recognize the complexity of the task at hand, based upon the clinical practice that I follow. I also have to be objective and push back a bit on my own personal bias, and simply state that I sort of feel that we're putting the pressure on the FDA to approve a combination that is completely impacted by biomarker testing or genetic testing.

Certainly, at least in my mind, I think that our deficiencies as clinicians and/or in our clinical setting as we practice are part of the result of this challenge. We're not testing properly. We don't do do enough testing, if you will, recognizing in some patients we may not be able to actually get the data that we need, but certainly the lack of testing throughout the United

States puts a lot of pressure when you're thinking as to how you move forward with this important task.

So my question for AstraZeneca, perhaps -- and I didn't see that data. And if you did, I apologize; I missed it. I don't have personally a challenge when I think about the importance of a PARP inhibitor in the appropriate biomarker setting, and specifically I'm talking about patients with BRCA1 and BRCA2. Even though we recognize in our group and our field that the bulk of the patients with DNA repair deficiencies tend to be BRCA2 followed by BRCA1, the most exquisite people who benefit from these agents appear to be really BRCA2. Then I don't want to get into details of monoallelic or biallelic, but that is the case.

So my question to AstraZeneca is, could you, or have you, or do you know what is the genomic data for those with undetermined BRCA mutations, that 35 percent? And also, for those non-BRCA1, non-BRCA mutations, if you will, which is

54 percent of the PROpel data -- and by that I'm simply asking, if you have a known BRCA mutation, I'm interested in understanding are there any other DNA repair deficiencies than those patients may have that are different than BRCA1 and BRCA2? The same applies for the undetermined BRCA mutation patients.

DR. MASSACESI: I will call Dr. Harrington to start to address this question.

Please, Dr. Harrington?

DR. HARRINGTON: Thank you. Elizabeth Harrington, AstraZeneca, translational medicine. We conducted pre-planned biomarker testing for HRR mutation status based on the 14 genes that are approved by the FDA for monotherapy treatment for olaparib, based on the PROfound study.

If we could have the slide up, please?

This I think addresses part of your question about the prevalence of other alterations within the PROpel study. Eleven percent of patients have BRCA mutations; 29 percent of the patients overall had HRR mutations. This is very in line with the

data reported in the literature and indicates that the patients enrolled on the PROpel study are very representative of the broader patient population.

You mentioned particularly BRCA1 versus BRCA2. 9.4 percent of patients had BRCA2 mutations, 1.5 percent had BRCA1 mutations, and for biallelic loss, 93 percent of the patients in the study had biallelic loss of BRCA, so a very high percentage.

DR. MASSACESI: Maybe, Dr. Garcia, you would also be interested to see the outcome of the non-BRCA HRRm patients.

Dr. Thomas, do you want to rapidly show this data?

DR. THOMAS: Sure. Laurence Thomas, AstraZeneca. Slide up.

We did look at the patients, or the subgroup of patients within this study that didn't have a BRCA mutation but did have a mutation in one of the other HRRm genes that were part of the 14 genes in the panel that we used. The data is shown here, and I think probably the most relevant row of this

table to the question is the fourth row down, which looks at that HRRm subgroup, which excludes BRCA patients. This is limited by small size, but the estimates in that group are consistent with the overall non-BRCA population, and we think this is indicative of the fact that those individual genes don't predict response better than anything else in that population as a result of the MoA.

DR. MASSACESI: Dr. George, do you want to comment clinically what this impacts?

DR. GEORGE: Thank you. Dan George, Duke. I just want to clarify something, Dr. Garcia, that you said around your understanding of PARP inhibitors and BRCA, and I think this is one of the fundamental issues between the FDA's interpretation and our interpretation, and that has to do with the mechanism of action.

In this setting, this is not a monotherapy PARP BRCA biology and abiraterone biology. We believe and hypothesize from Study 8 that there's an interaction between the use of a novel hormonal agent and a PARP DNA damaging agent in this

setting. This is not a new hypothesis. This is something that we have done in prostate cancer for over 20 years in the case of using androgen deprivation therapy and radiotherapy, radiotherapy damaging DNA; androgen deprivation therapy making that androgen receptor signaling susceptible to that DNA repair issue.

So this really builds on a very long well-established hypothesis of the interaction between androgen receptor signaling and DNA repair, and the evidence here really does suggest that in the setting of BRAC2 mutation, that effect is supercharged, but it's not to say that the effect is limited to the BRCA2 mechanism. It's not.

DR. MASSACESI: Thank you.

DR. GARCIA: Thank you, Dr. George, and thanks, AstraZeneca.

Let's go on with the committee.

Dr. Madan, you have a question or a comment?

DR. MADAN: Yes, two questions. I'll let you decide if I get to ask both now. I know other people have comments. Ravi Madan, National Cancer

Institute.

I view this question here today as a classic combination versus sequencing question, and we've been asking this question in oncology for years, if not decades. This makes overall survival a key readout, but the overall survival readout is only relevant if a substantial proportion of the patients on the control arm went on to receive a PARP inhibitor, which wasn't part of the study design.

This is especially key in the group in the control arm that were BRCA positive because if patients that were BRCA positive never received a PARP inhibitor, we know their outcomes are going to be worse, and we know that from well-established phase 3 data. So it really would call into question any supporting role of the OS component to this discussion to validate the PFS.

My concern here is high because I worry that patients that were accrued on this study, that were accrued outside the United States, in the control arm, with known BRCA2 positivity, may be in a

setting or an environment where a PARP inhibitor was not an approved standard of care. So unless I missed it, and I apologize if I did, I think this is a key part to this question when we're talking about validating PFS with OS. Thank you.

DR. MASSACESI: Let me start to address it, first of all, methodologically. The study did not allow crossover because OS was a key secondary endpoint. So you're right; very few patients received PARP inhibitors upon progression despite, of course, in quite a few patients, their status was known.

Anyway, going back to the core of your question to address one important aspect that's being presented in the core presentation, half of these patients -- or less than half of these patients -- are going to receive second-line therapy for several reasons, and the sequencing question also needs to take into consideration this. Yes, we are comparing and we are discussing a combination that is exploiting increased DNA damage by two different agents, a PARP inhibitor

plus an NHA, and that's a sequence that I imagine you refer to an NHA followed by a PARP inhibitor, where the PARP inhibitor monotherapy will be exclusively used in the context of an HRR pathway-activated setting, so in a minority of patients, so probably this is an important aspect.

I would ask Dr. Armstrong to come in and also provide his clinical perspective on this.

DR. ARMSTRONG: Good afternoon. Andrew Armstrong, a medical oncologist at Duke and one of the PROpel principal investigators. I'm a paid consultant to AstraZeneca but have no relevant interest in the outcomes financially of this meeting.

As a PROpel investigator, when the study was designed, the data from PROfound was emerging as a monotherapy for the improved survival in BRCA-mutated patients. When patients and investigators had progression, the results of their genetic testing was made available upon request to the treating investigator and to the patient to make informed decisions about their subsequent therapy,

and thus, a BRCA-mutated patient would be revealed to be BRCA mutated at progression, and then could receive olaparib, which was offered as part of standard of care, depending on the region of the world and the availability of that therapy. However, the investigator could choose docetaxel, cabazitaxel, radium, or whatever appropriate therapy; and as we show, the standard-of-care therapies were appropriate and equal across the treatment arms. Thank you.

DR. MADAN: So can I clarify, though? Do you guys have -- or can you share with us the data, the proportion of patients that went on from the control arm to get a PARP inhibitor we know are superior to other standard-of-care options in that population?

DR. MASSACESI: I think, Dr. Toms, you have these data?

DR. TOMS: Could I just clarify, you're looking for the data in the all-comers' population or in those with the BRCA mutant?

DR. MADAN: Either one, I guess, but I'm

more interested in the BRCA2's, or the mutated, because if they didn't get a PARP inhibitor, we know they're going to do worse.

DR. TOMS: Sure. We don't have that to hand. We can try and get that to you after the break. We do have the data from the all-comers. Actually, we do have it. I apologize. We do have it. So if we'd go slide up, 16?

Here's that data. So you can see this is restricted to the BRCA mutant subgroup, and the number of patients on the control arm, placebo plus abiraterone, who went on to get a PARP inhibitor, but just one patient.

DR. MADAN: Okay. So that's the answer, then.

DR. TOM: Yes. Thanks.

DR. MADAN: DR. Garcia, I said I had two questions, and it kind of leads into one of the answers that was provided; if I may ask a second question?

DR. GARCIA: Go ahead, Ravi.

DR. MADAN: The second part to this is, is

that data -- which to me is kind of shocking in clinical practice that only, I believe, 38 percent of patients get second-line therapy -- I would look at the publication dates of those publications, and that, really, the question you're asking in that analysis is, are you giving chemo to patients after first-line progression on abi or enza because the data come from 2020 and 2021.

I think that's not really the question for the mutated population, where I don't think anybody argues there's benefit. The question, really, we should be asking correctly is, if you know a patient is a BRCA mutant, how many of those patients go on to get a subsequent PARP inhibitor? Again, it goes back to the fact that the question here before us is kind of artificially generated in the United States, where we have the opportunity to sequence these therapies. So it's not abi and olaparib now or never; there's a sequencing opportunity.

I guess I'll ask the the applicant if they want to clarify if they have any data that actually

talks about BRCA2 patients not getting PARP inhibitors after abi or enza, because I think that's really the key data point, because I think the data that was shown was probably largely chemotherapy, and we all know there's a little bit of a reluctance to use chemotherapy in older patients with prostate cancer. Thank you.

DR. MASSACESI: I don't think we have data supporting this question, clinical data.

Dr. O'Connor, do you want to maybe comment molecularly, and then maybe Dr. Shore, if you can step up.

DR. O'CONNOR: Mark O'Connor, chief scientist in oncology at AstraZeneca. I think the key point here is that we see interplay between PARP inhibitors and the novel hormone agent. So we get more DNA damage when they're combined together, as opposed to giving sequencing, where you'll have the benefits of one agent alone, and then another. And obviously, those benefits with a PARP inhibitor primarily as a monotherapy are going to be in HRR mutant. So we think the combination of these two

agents together will actually be more effective, both in BRCA backgrounds, but also it will be effective in the non-BRCA and non-HRR background.

So that's the basis of the combination. If those patients, I guess, were given that combination up front, then they should have that combination back [inaudible].

DR. SHORE: Neal Shore, GenesisCare; a really important observation, Dr. Madan. You're absolutely right. We have substantial contemporaneous data that less than 50 percent of patients throughout the journey of mCRPC in North America ever received a taxane, which is shocking. And the data that I presented is contemporaneous data regarding the lack of second- and third-line therapies, which is why -- in tandem to that, and our lack of testing in the real world -- for all the challenges that we ascribe to you -- slide up, please -- this really speaks to, at least from my perch, and both from a research standpoint, and a community standpoint, and a real-world standpoint, it's being able to optimize with a combination

therapy in first line and having that full-throated discussion with patients reviewing the benefit-risk.

DR. MADAN: Okay.

DR. MASSACESI: Thank you.

DR. MADAN: I would just confirm, though, that this data was from pre-PARP approvals in prostate cancer largely; correct?

DR. MASSACESI: Yes.

DR. MADAN: Okay. Thank you.

DR. GARCIA: Thank you, Dr. Madan.

Dr. Nieva?

DR. SUZMAN: Could the FDA respond as well? This is Daniel Suzman, FDA. Actually, could you bring up backup slide 46 of FDA?

DR. GARCIA: I'm sorry. Who is this speaking?

DR. SUZMAN: Sure. This is Daniel Suzman, FDA.

DR. GARCIA: Okay. Go ahead, and then we'll go to Dr. Nieva.

DR. SUZMAN: Sure. Great. Thank you.

Could you bring up backup slide 46, FDA? Great. Thank you.

This is just one additional way of looking at the post-progression therapy per Dr. Madan's question, again, broken down by our three subgroups by likelihood of BRCA mutation status. We also included post-progression receipt of platinum compounds since those are likely effective in a patient's BRCA mutation. Thank you.

DR. GARCIA: Thank you.

Dr. Nieva, go ahead.

DR. NIEVA: Thank you, Dr. Garcia. My question is for Dr. Weinstock.

The FDA has chosen to frame this question to be whether or not the drug should be restricted to BRCA mutants and not to the broader population of homologous recombination deficient patients. I'm wondering, what is the FDA's rationale behind not including the larger patient population, where there doesn't seem to be any disagreement that they might benefit from olaparib as the framing question today?

DR. WEINSTOCK: Thank you. Can you clarify your question? Are you asking about why we chose BRCA as the basis for our question rather than HRR mutation?

DR. NIEVA: Yes.

DR. WEINSTOCK: Okay. So I would refer to our backup slide 39, which was presented, to some extent, by the applicant. It's backup slide 39, and this reviews the rPFS by investigator assessment and overall survival by BRCA and HRRm as subgroups, and then it looks at the non-BRCA-mutated HRRm subgroup, which is, again, the patients with HRR mutation minus the patients with BRCA mutation; and you can see that the benefit in that particular subgroup is not very clear. The rPFS hazard ratio is 0.8 and the overall survival hazard ratio is 1.02.

So when we were looking to choose a subgroup that appeared to be contributing the most to efficacy, BRCA had the most biologic plausibility, and also the numbers really looked like the efficacy was primarily in that subgroup. That's

not to say that there aren't patients with HRR mutations who may be benefiting; we just haven't characterized them adequately in this trial. And you can see those results for the non-BRCA-mutated HRRm subgroup here, which is the final column on the right, showing our concerns, which is why we didn't go with that as the primary basis of our question.

Does that answer your question?

DR. NIEVA: It does. I would have liked to have seen the analysis when you're looking at the patients who were deemed to be BRCA negative. Then there was an unknown finding or deemed to be BRCA indeterminate as to what the homologous recombination status would have been. I would have liked to have seen a parallel analysis as detailed as you provided before, but I understand the rationale, so thank you.

My second question is for the AstraZeneca team, specifically related to toxicity. You showed a quality-of-life analysis on slide CS-5, but you included it for the entire population and didn't

restrict it to the BRCA negative population. As you know, quality of life has multiple factors that can impact it, including efficacy, as well as toxicity.

The question here today is whether or not the BRCA negative patients have unnecessary toxicity. Do you have quality-of-life analysis for the BRCA negative or even the HRD negative patients who were treated in combination?

DR. MASSACESI: Yes, sir, we do.

Dr. De Champlain, do you want to come and present this data, please?

DR. DE CHAMPLAIN: Andre De Champlain, AstraZeneca, clinical outcomes assessment. Slide up, please. This is essentially replicated analysis from the one that was presented in the safety data set, which again shows mean FACT-P total scores across the duration of the study, and on the right, overall change from baseline values in both treatment arms for this particular non-BRCAm and the aggregate population.

Again, similarly using a clinically

meaningful value of 10 or less, which was suggested in the literature and used in other studies, we see that neither treatment arm actually meets that threshold, and more importantly, the difference between the two, again, is very, very similar, less than 1 point or around 1 point.

DR. NIEVA: Thank you. This concludes my questions.

DR. MASSACESI: Thank you.

DR. GARCIA: Thank you.

Dr. Rini, do you have a question or a comment?

DR. RINI: I do. Thank you. Brian Rini, Vanderbilt. It seems to me the main issue at hand here is inclusion of that middle 35 percent of patients, those uncertain or indeterminate patients, where the sponsor's including them in the non-BRCA group, and FDA is not including them and only including the double-negative patients, so to speak.

The sponsor may have alluded to this, and I may have missed it, but I'm not sure we saw the

data; that if any sensitivity analyses have been done looking at that group and estimating, well, gee, what if 10 percent were BRCA mutated as in the ITT? What if it was 15? What if it was 20? And to look at outcomes based on a hypothesized percentage of BRCA mutant that could have diluted that subgroup or contributed to its benefit.

DR. MASSACESI: Dr. Rini, allow us to answer this question before showing you why we believe that a minimal number of patients would have been misclassified in that subgroup of undetermined or negative unknown; specifically positive DNA testing and the methodology that we used to ultimately end up at a very small number of six, and then we can show you the sensitivity analyses that Dr. Toms alluded to during his presentation to see the impact, eventually. If some misclassified patients would have been taken into consideration, ultimately, the outcome of this subgroup would not be changing and doesn't explain why it's so different compared to double-negative.

Please, Dr. Liu, if you can start with the

first question.

DR. LIU: Yuzhen Liu, AstraZeneca, precision medicine. Slide up, please. PROpel provided very rigorous testing. We used FDA-approved tumor tissue and the ctDNA test, and we determined 98 percent of patients for the biomarker status. In the non-BRCA subgroup, we have 226 patients with ctDNA results, and when we look at the patients with both test results, we have seen very high, overall, agreement, which is 94 percent, so we calculated the probability of ctDNA to miss BRCA mutant patients and to be included in the non-BRCA subgroup. So we actually used two different approaches to determine better probability.

One approach is to look at positive percent agreement. As FDA presented to you, the positive percent agreement between the two tests is 74-to-80 percent, so in PROpel, it's 74 percent; so ctDNA could miss 26 of BRCA mutation detected by the tissue test, taking into account 11 percent BRCA mutant prevalence in mCRPC. So the probability for the ctDNA to miss BRCA mutant

patients is 26 percent times 11 percent, and that is around 3 percent.

Another approach to estimate the probability is to look at the negative predictive value. We have seen 97 percent of non-BRCA patients determined by the ctDNA test and were confirmed by the tumor tissue test, and again, indicates 3 percent of patients could be misclassified by the ctDNA test. So out of 226 patients that only have ctDNA results, we say around 6 patients could be misclassified. If those 6 patients were reclassified, it's not going to change the results. I would also point out, patients who had ctDNA test results only also tested by germline test, they have confirmed to have no germline mutation.

DR. RINI: Could I ask a follow-up question to that?

DR. GARCIA: Please go ahead.

DR. RINI: So that non-concordance rate of 26 percent -- and I don't know this primary data -- is that in this same setting or is it in a a different setting? That's my first follow-up

question.

DR. LIU: Thank you. It is in our PROpel non-BRCAm aggregate patient subgroup.

DR. RINI: Okay. Then if it's really only 6 patients, if you look at the hazard ratios and the curves, boy, it looks like that indeterminate group is kind of in the middle. It looks very different than the other. So if it's only 6 patients, why is it different?

DR. TOMS: Let me just address that question a little bit, and I think your initial question asked about sensitivity analyses around this. If you go to -- slide up -- ES-27, just to remind everybody, there are two basic groups of non-BRCA patients, the double-negative group and the negative unknown group, and together we assess those as the non-BRCA aggregate group. The FDA has restricted that classification to the double-negative group only. In that single-negative group, you may remember from the presentations that the efficacy looks to be a lot better than the double-negative group. The

traditional explanation for this is false negative patients, misclassified patients, that truly have a BRCA mutation residing within that negative unknown group.

Now, as Dr. Liu has explained, from concordance data within the study, we have an estimate of what that false negative rate may be. It's around 3 percent. So what we did was sensitivity analysis to see what removing 6 patients from that group would do to the estimate of treatment effect within the negative unknown population, and that's what's shown on this slide.

We used two approaches to do that. The first is the FDA-approved method, whereby we took those 6 patients out at random, and that's what's shown in the middle column there. The primary effect estimate is 0.7, and when you take 6 patients out at random, the hazard ratio remains the same. We doubled the false negative rate to make a conservative assumption, and we got the same result.

But clearly what we really wanted to do is

try and identify the actual BRCA patients within that negative unknown group and then remove them. It's impossible to do that on the basis of the test results because we didn't have that data by definition. So to take a conservative approach, we assumed that those 6 patients would be equally distributed between the test and the control arm, and we took the three best performing patients from the test arm and the three worst performing patients from the control arm and re-estimated the effect size in that group, and got 0.76.

We then made a further, highly conservative assumption and doubled the false negative rate again, and took six best performing patients out of their experimental arm and the six worst from the control arm, and the hazard ratio went to 0.87. The conclusion of this analysis is that even with these very conservative assumptions, we're demonstrating a true effect independent of misclassified BRCA patients within that population.

DR. MASSACESI: Thank you.

DR. RINI: Thank you. I'm all set.

DR. SUZMAN: Sure. Actually, this is Daniel Suzman, FDA. I'd like to invite our FDA statistician, Dr. Erik Bloomquist, to address this question as well, and if you wouldn't mind bringing up FDA backup slide 42, please.

DR. BLOOMQUIST: Thank you, Dr. Rini, for the question. Yes, I think that's part of one of the key issues here, is if we are able to identify the BRCAm status from the majority of patients, we wouldn't be left with this undetermined subgroup as well.

For our analysis, we have done similar sensitivity analyses as what AZ did, and what we did is we hypothesized based upon the numbers here of 10 patients in the treatment group and test patients in the control arm group. What we had done is we had selected the most favorable patients from the control arm group and the least favorable from the treatment arm group, and the idea was to come up with a worst-case analysis to say that if we identified the BRCAm patients very specifically, how would the all-other groups really favor. The

all-other group would mainly represent the non-BRCAm subgroup here, and we did find that the OS hazard ratio in the all-other subgroup could move from 0.92 up to roughly 1.02.

So based upon a worst-case analysis, we weren't able to rule out an OS above 1 based upon that sensitivity analysis. There are other sensitivity analyses that can be conducted. I think one of the reasons that we're faced with this issue here is there is a large number of missing tissue tests where they were conducted, and it's difficult to assess the missing data in light of that. So I think that's one of the main reasons that we're here today, is the large number of missing samples, and the sensitivity analyses have to also be taken into account with that. Thank you for the question.

DR. GARCIA: Thank you.

Does the FDA have additional comments?

(No response.)

DR. GARCIA: Dr. Harzstark, do you have a question or comment?

DR. HARZSTARK: Thank you. Andrea Harzstark, Kaiser Permanente. This question is for AstraZeneca.

Delaying clinical deterioration has been presented as a reason why PFS is meaningful in the non-BRCA population in the absence of an overall survival signal, so getting at the question of delaying chemotherapy toxicity and improving quality of life, do you have data specifically on pain, meaning improved or delayed in this population in the non-BRCA subset? Thank you.

DR. MASSACESI: I would ask him Dr. De Champlain to show the data, and maybe Dr. Armstrong to come and comment specifically on the clinical perspective, please.

DR. DE CHAMPLAIN: Slide up, please.

As we wait for the slide to show up, just a few points of clarification. Slide up, please.

This particular endpoint was a conjunctive endpoint, and what I mean by that is it was defined either by an increase in response to BPI, Brief Pain Inventory, short form, item number 3, the

worst pain in the last 24 hours and/or initiation or increase in opioid consumption. Secondly, this is a confirmed time-to-pain progression definition; that is to say that patients needed to demonstrate it at two consecutive visits. Both of those conditions were negotiated with the agency in the PROfound study.

Now, before we actually look at the result, which is shown here, it's important to point out that the data maturity for this time-to-pain progression endpoint was very low. As you can see in the box on the right, about 16 percent of patients, overall, met the endpoint, and there was no differential outcome for time-to-pain progression between both treatment arms.

DR. MASSACESI: Dr. Armstrong, please?

DR. ARMSTRONG: Andrew Armstrong, Duke University. In my clinical experience managing men with mCRPC, the use of opiates and pain progression tends to be a very late event in the life of a patient and tends to occur in the last 6-to-12 months of life. Most of our

quality-of-life data capture the experience of patients during the PROpel regimen, which was the first 3 years; and thus, many patients did not experience a pain progression event, skeletal event, or time to opiate use, but they did have a substantial delay in their need for cytotoxic chemotherapy regardless of a BRCA mutation.

DR. MASSACESI: Thank you.

DR. HARZSTARK: Thank you very much. That's all for me.

DR. GARCIA: Thank you.

Dr. Vasan, I apologize. I missed you earlier, but now I can see you.

DR. VASAN: Hi. Neal Vasan, Columbia University Medical Center. I wanted to ask a follow-up question to Dr. Rini's point about, really, the nature of the dichotomization. I agree with Dr. Rini's assessment that this is really the key distinguishing analysis factor between the FDA and the applicant and, again, about this group that the applicant is classifying as ctDNA negative but tissue NGS unknown, classifying that as non-BRCA

mutant versus while the FDA is calling this the indeterminate group.

I know the applicant was discussing, in the real world, the differences between the single testing versus the double testing, and I understand that, but I would also think that in the real world, many oncologists would consider this group indeterminate in the sense that additional testing might be required to determine if they're BRCA mutant or non-mutant, but relative to if they're a candidate for a PARP inhibitor, and under normal circumstances, we might call that non-BRCA mutated.

So the question really here is having to do with this additional testing, because I think in the real world, a patient who is ctDNA negative but tissue unknown, that would be the type of patient, whereas an oncologist, we would consider a second biopsy or retesting. So I'm wondering if that was done on this trial for patients who had an initial tissue NGS unknown test. And also for the patients who were categorized as BRCA mutant or BRCA non-mutant, was that on the basis of just a single

tissue test or multiple retestings of the tissue was that allowed?

DR. MASSACESI: Please, if you're going to address what was done in the protocol, Dr. Harrington rapidly, and then I would like Dr. George to answer the question because there is a lot of components here related to the clinical aspects of this testing.

Very rapidly on the protocol.

DR. HARRINGTON: Elizabeth Harrington, translational medicine, AstraZeneca. Slide up, please. Of those patients that we were unable to get a tumor test result from the initial test, we requested an additional sample from the clinical site. This was provided for 24 percent of patients. Of those patients, only 10 patients had known biomarker status after a second test, and all of those 10 patients had BRCA or HRR mutations that were identified by the ctDNA.

An additional point that I'll raise, which my colleague, Dr. Liu, mentioned previously, is that we did analyze all patients using a germline

test where samples were available, and for those patients with ctDNA-only results -- slide up, please -- a hundred percent of those patients with ctDNA only were non-BRCA mutant by the germline test, which is an FDA-approved test.

DR. GEORGE: Dan George, Duke University. Yes. This is, I think, a really important point because the reality is that what was done in PROpel was still a tremendous comprehensive assessment by three different tests -- germline, ctDNA, and tumor tissue -- in 98 percent of the patients. So this sort of undetermined or unknown isn't because we didn't test all three assays in the patients; we did. We had assays in all three done, and we still had, despite that effort, 35 percent of patients that we could not determine, by both somatic tests, a negative BRCA status, so even though they were negative by both, one test as well as by germline.

So you're dealing with, I think, really the best case scenario, which we won't be able to replicate in the real world. These patients become metastatic castration-resistant, and we're on the

clock. They're ready to go; "Okay, we've got to change therapy." They may not be symptomatic that much, but they're anxious, and nervous, and want to get started. And yes, we can go ahead and send these tests off, but getting an additional biopsy is very low yield. Most of these patients are bone disease, which is sclerotic bone that we're not going to get tissue from, or the pelvic lymph nodes, which we can't reach. So by and large, we're limited to this kind of archival tissue or blood testing that was done in PROpel.

DR. MASSACESI: Thank you.

DR. VASAN: Can I just ask a follow-up question? Based on the prior speaker's analysis in the slide, those additional patients who had second-round testing, just to clarify, was that part of the initial analysis that AZ is presenting now, or is there a subsequent analysis that integrates those patients?

DR. MASSACESI: Dr. Harrington?

DR. HARRINGTON: Elizabeth Harrington, mCRPC, AstraZeneca, translational medicine. Slide

up, please. The analysis was conducted after database lock. The additional 10 patients who were determined as BRCA or HRR mutations were actually included in our HRR mutation group. So the data that we got from the additional biomarker analysis of the retested samples was in accordance with the data that we'd seen from the ctDNA, so they weren't part of the data that was shown.

DR. VASAN: I'm sorry. They were or they were not part? I apologize.

DR. HARRINGTON: They were not.

DR. VASAN: They were not.

DR. HARRINGTON: This retesting was done after database log, so it's not part of the analysis shown --

DR. VASAN: Okay. Thank you.

DR. HARRINGTON: -- and would not have changed the results of the study because the data was concordant with the ctDNA assay test result.

DR. VASAN: Okay. Thank you.

DR. MASSACESI: Thank you. Hopefully the question is answered.

DR. GARCIA: Dr. Rosko?

DR. ROSKO: Hi. Ashley Rosko, Ohio State. My question is for the applicant. It is a follow-up question to Dr. Nieva's health-related quality-of-life question. My question is in response to understanding the quality of life, the FACT total scores, for patients that were BRCA mutated versus BRCA non-mutated, and particularly for the patients that were receiving olaparib, the differences in the scores over time.

Can the applicant clarify that data?

DR. MASSACESI: I would like to invite to the podium Dr. De Champlain to start to answer the question, please.

DR. DE CHAMPLAIN: If I understand, again, just to clarify, the question is comparing health-related quality of life longitudinally for non-BRCAm versus BRCAm patients. Is that the question?

DR. ROSKO: Specifically, yes.

DR. DE CHAMPLAIN: Yes. Thank you.

Slide up, please. Again, this slide shows

the mean FACT-P total score across the duration of the study for both treatment arms, for the non-BRCAm in this particular instance, and as I pointed out earlier, the difference between both treatment arms was quite small, only about a 1-point difference, neither reaching the threshold that we had set for clinically meaningful deterioration, again, based on the literature value of 10 points, as I pointed out.

Slide up, please. Yes. If we now look at the other group, the same analysis, but for the BRCAm aggregate subgroup, the story is the same overall in the sense that the means were quite comparable. The differences were a little bit larger, 3.64 points here, but again, well below the threshold of 10 that we had set, with a change of plus 2.4 for the olaparib arm and a change of minus 1.21 for the abiraterone arm. Again, the sample sizes are quite small here, which accounts for some of the large standard errors shown, towards the end especially.

DR. ROSKO: Question is answered.

DR. MASSACESI: Thank you.

DR. GARCIA: Dr. Madan?

DR. MADAN: Ravi Madan, NCI. Just a follow-up question for the sponsor, for the applicant. Lots have been made about the delay for chemotherapy, and I'm sorry if I missed it if you guys showed this. But there's a 30 percent increase in myelosuppression with the PARP inhibitor of a 4-fold increase in blood transfusions.

Does your delay, in terms of time to chemotherapy, control for that in any way; in other words, for patients subsequently delayed for chemotherapy because we needed to wait for blood counts to recover back to safe levels? Thank you.

DR. MASSACESI: I would like, first of all, to ask Dr. Turner to clarify the safety report because I think FDA aggregated the myelosuppression term and probably is not the best way to look at these data. It would be probably more helpful to see when they are separated by anemia, and eventually in neutropenia, lymphopenia, and so on.

Dr. Turner, please?

DR. TURNER: Simon Turner, patient safety, AstraZeneca. I think you mentioned myelosuppression but, really, we're talking about anemia specifically with olaparib, and I think we've got a slide that shows the effect on the different cytopenias.

Could we have slide up, please? Fifty-four percent of patients experienced a cytopenia event of any grade; thus, the majority of this, 49 percent, is anemia. To a much lower degree, you see neutropenia around 10 percent and thrombocytopenia around 7 percent, so really we're talking about anemia.

From the protocol, if we have prolonged cytopenias over 30 days, patients will need to discontinue drug, so a very low incidence of discontinuations; and therefore we can conclude from this that these events are very reversible in care with patients treated with olaparib.

DR. MASSACESI: Dr. George, can you put also the safety profile in terms of hematological

toxicity, in the context of when you treat patients, what it really means?

DR. GEORGE: Dan George, Duke.

Could I get the slide with the timing of anemia and toxicities? So to answer your question, this is a real concern that happens early in the course of treatment with olaparib. Within the first 3 months is where we see the bulk of the anemia in any of those -- particularly grade 3 -- anemias that require transfusion, and as you can see, most of those events are happening within the first 3 months, and then there's a much lower incidence.

So by the time patients are progressing on this regimen, mean is really not the issue. By that point in time, we've either lowered the dose, interrupted the dose, or if there were some patients that just couldn't tolerate olaparib, they stopped it. So we did have some discontinuation of olaparib, but all of those events were worked out relatively early. So by the time patients were on the back end of this, developing disease

progression, this wasn't really affecting that next line of therapy.

DR. MADAN: Just a follow-up question there again. I feel like a statistician here. You're dating it more skewed as you've been on the therapy. A patient who's tolerating it well doesn't come off at 6 months. So the longer you go, you've already selected out the patients that are tolerating it better, and maybe this question is more relevant for the patients that don't tolerate it; in other words, if you come off in the first 6 months and you can't go to chemotherapy, that's a bigger problem for those patients. It's kind of why it would be good to tease out from this data how cytopenia has impacted your delay for chemo question.

DR. GEORGE: Sure. It's a great point, and we recognize when we do an intention-to-treat population, first off, all metastatic castrate-resistant prostate cancer populations are heterogeneous. There are no homogeneous metastatic castrate-resistant populations. And secondly, even

with abiraterone, we see a spread of responders and non-responders, so you're going to have that. In fact, when you look at these curves, these Kaplan-Meier curves for rPFS, they kind of overlap to start, and then they separate out a little bit later, even with the BRCA-mutated population.

So the reality is absolutely what you're saying. There's a group of patients that this is just not working in, either abiraterone or olaparib, and they're probably going on, and they may get chemotherapy and they may not. We don't see a difference in the early survival associated with that, so I don't think it's an ultimate detriment to that population. It's just that it's probably not benefiting that worst 10 percent or so.

But then as we work through this and as the vast majority of patients are able to tolerate this regimen, that's where we start to see the anemia under control, the toxicities resolved, and the patients maintaining that quality of life without any kind of cumulative build-up of toxicity,

reflected both in the patient-reported outcomes.

DR. MASSACESI: Dr. Madan, let me also address more specifically -- slide up, please -- your question. There was not an impact on PROpel at the time of the first cytotoxic chemotherapy or death because you see 31, and numerically there were slightly less patients that received cytotoxic chemotherapy in the olaparib-abiraterone arm compared to placebo-abiraterone. Overall, when you look at the subsequent anti-cancer treatment, the other issue, it's still very much in favor of the investigational arm, looking at the totality of the data. So hopefully this is answering your question.

DR. MADAN: It does, and it goes along with your data that says that the olaparib toxicity is reversible. It's just important to contextualize the delayed chemotherapy benefit that's being presented here, but thank you.

DR. MASSACESI: Thank you.

DR. GARCIA: Thank you.

In the interest of time, we're going to have time for one additional question and final.

Mr. Bui?

DR. BUI: Hi. This is Dr. Bui from Pyxis Oncology. This question probably goes to Dr. Turner from AstraZeneca.

In slide 30, the FDA slides, the FDA raised the high risk of thromboembolic events. I don't see that addressed in your presentation other than anemia and GI toxicities. Can you speak a little bit more about thromboembolic events in PROpel and how it was managed?

DR. MASSACESI: Please, Dr. Turner, if you can reach the podium?

DR. TURNER: Simon Turner, patient safety, AstraZeneca. We have a slide on the venous thromboembolic events in PROpel. The instance of VT events in PROpel was similar to that reported with other olaparib studies in prostate cancer. Venous thromboembolism is identified as an adverse reaction for olaparib based on the data from the PROfound study, a monotherapy study in prostate

cancer, on the basis of that as an adverse reaction to the USPI, and also a warning was included on it.

We know that cancer patients are at high risk of developing VT events, especially prostate cancer patients treated with androgen deprivation therapy. The data in PROpel here, there are 8-and-a-half percent of patients who had an adverse event of thromboembolism on the olaparib plus abiraterone arm versus 4 percent on the placebo arm. And also, just to note, about half of the serious VT events in PROpel were asymptomatic, detected incidentally on radiographic imaging, and the vast majority of patients who developed a VT event recovered with standard medical care, and they're able to continue treatment.

DR. BUI: Thank you. No follow-up questions.

DR. GARCIA: Thank you.

I think it's time for a break. It's 2:02. We're going to take a 28-minute break. Panel members, please remember that there should be no chatting or discussion of the meeting topic --

DR. JANKOWSKI: Excuse me. Dr. Garcia., I apologize to interrupt.

DR. GARCIA: Go ahead.

DR. JANKOWSKI: FDA would like to make comments. Thank you.

DR. GARCIA: Oh, I didn't see them. Thank you.

DR. JANKOWSKI: No problem.

DR. SUZMAN: Thank you. This is Daniel Suzman, FDA. If you wouldn't mind bringing up FDA slide 23? I'd just like to respond to the applicant's point that early discontinuations did not affect survival, and I'd like to bring up the slide for the 89 percent of the ITT population in whom there was no BRCA mutation detected. Again, the hazard ratio for OS was 0.92, but I'd just like to point out that the placebo plus abiraterone arm, in blue here, was actually doing superior to the combination arm for the first 24 months. So to that end, it may be that early discontinuations did affect overall survival in this group. Thank you.

DR. GARCIA: Thank you.

I'm going to let the AstraZeneca folks answer. If you can be brief so we can go on a break because we're quite behind. That would be great.

DR. MASSACESI: Yes. Thank you. Just to point out that AstraZeneca does not see any detriment in the treatment of abiraterone plus olaparib, even in the non-BRCA and even eventually in the non-double-negative population, simply for the fact, as we hopefully allotted in the core presentation, there is not enough evidence that the safety profile of olaparib can induce this detriment. Slide up, please. There was only an imbalance when you look at the real important safety events, the treatment-related events.

If we can have slide up? This is related to the COVID-19 deaths, and COVID-19, of course, was unfortunately an event that was unpredictable. The study did not take into consideration randomization. One-third of the patients were not vaccinated. We were really in the middle of the pandemic. This is a sensitivity analysis that we

run, looking at overall survival, censoring the patients with COVID-19 that unfortunately died. At the time of the last visit, they were alive. These were, if you recall the presentation of Dr. Turner, 12 patients in the olaparib and abiraterone arm and 3 patients in the placebo arm, and there was a risk factor baseline for the outcome of COVID, independent of course of the treatment that they received in the study.

When you look at the hazard ratio, I want to point out the bottom of this slide. You have overall survival, primary analysis, and then the sensitivity analysis censoring the COVID deaths, and you see that the hazard ratios are changing, and they're changing, of course, becoming better. The FAS is going to 0.77, and it's improving also in BRCA patients, but more importantly, it is improving also in non-BRCA patients, aggregate and double-negative, and in double-negative, it actually goes below 1.

So the safety profile and also the subsequent treatments, the access to the

subsequent, the cancer treatment that we discussed just a few minutes ago, are two very critical factors that explain the known detriment of olaparib on top of abiraterone, even in the non-BRCA population. So we do not believe that this regimen can harm patients, even in the non-BRCA subgroup. Thank you.

DR. GARCIA: Alright.

We will now take the break. It's still 2:06. Panel members, please remember that there should be no chatting or discussion of the meeting topic with anyone during the break. We'll resume promptly as 2:35; again, 2:35 p.m. Thank you.

(Whereupon, at 2:06 p.m., a recess was taken, and meeting resumed at 2:35 p.m.)

Open Public Hearing

DR. GARCIA: 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 applicant, its product, and if known, its direct competitors. For example, this financial information may include the applicant'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.

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

Speaker number 1, please unmute, and you may turn on your webcam. Will speaker number 1 begin and introduce yourself. Please state your name and any organization you are representing, for the record. You have five minutes.

DR. KILARI: Good afternoon. My name is Deepak Kilari. I'm a genitourinary medical oncologist at the Medical College of Wisconsin in Milwaukee, Wisconsin. Today I am reading a statement from Dr. Rana McKay from the University of California San Diego, who could not attend the

meeting. Thank you.

"The PROpel study was a randomized, phase 3 study, testing the efficacy of the combination of olaparib plus abiraterone compared to placebo plus abiraterone, in patients with metastatic castrate-resistant prostate cancer unselected for homologous recombination repair gene alteration status. The primary endpoint of the study was investigator-assessed radiographic progression-free survival, and the key secondary endpoint was overall survival.

"The trial was a positive study and met its primary endpoint of improved radiographic progression-free survival with combination therapy. Additionally, while the trial was not statistically powered to assess overall survival, there was a positive trend for improved overall survival in the intent-to-treat population with the HR of 0.81. Additionally, overall survival favored combination therapy in all subgroups, including homologous recombination repair mutated with the hazard ratio of 0.66 and the homologous recombination repair

non-mutated with the hazard ratio of 0.89. Other secondary endpoints favored the combination and quality of life is similar between the two arms.

"The proposed study met the objectives it was designed to achieve. As with all therapies, location and clinical practice are dependent on many factors, including disease characteristics, mutation status, patient factors, and other variables. Clinicians integrate the trial data, including subgroup analysis, with the disease characteristics and goals of the patient before them in clinic to select an optimal treatment strategy for a given patient. Patients and clinicians desire to be given the choice to select the optimal therapy based on thoughtful discussion and shared decision making.

"It is critical that patients and clinicians have this choice to be able to select the best treatment regimen for the given patient, based on solid clinical trial data. Thank you for your time."

DR. GARCIA: Thank you, Speaker number 1.

Speaker number 2, please unmute, and you may turn on your webcam. Will speaker 2 please begin to introduce yourself? State your name and any organization you are representing, for the record. You also have five minutes.

MR. SANTORO: My name is Leonard Santoro. I have no financial interest in the outcome of this whatsoever, and I'm just representing myself as a patient.

I want to thank the members of the committee for allowing me to address you today. I am a patient in the PROpel study at Duke Cancer Center under the care of Dr. Dan George and his team. I was first diagnosed with prostate cancer in 2013 when I was 61 years old. My prostate was removed, and I had a course of radiation. I was then treated with Zante.

I joined the PROpel study in October of 2019. At that time, I had a bone scan that showed abnormal foci, radiotracer identification in the sacrum, lumbar spine, right iliac bone, and thoracic spine, new from prior scans. My PSA was

20.

The drug started taking effect very quickly. My PSA dropped by 90 percent in the first 3 months of the study. It was undetectable by September 2020 and has remained that way. My last bone scan, December 2022, showed no suspicious foci of increased radioactivity to suggest osseous metastatic disease.

To say that this treatment saved my life would almost be an understatement. When I first entered the study, I was sure I was heading for a swift and painful death and that I would never see my granddaughter grow up. This has all changed dramatically. My health is good, the treatment has had minimal side effects, and has been easy to manage. I recently found out that I was on the combination therapy. I hope the committee will support the approval of this combination so that more patients can benefit from this treatment. I am glad to be part of the development of this successful treatment of prostate cancer, and that it will enable other patients to have a future they

can look forward to.

That's my statement, and if anybody has questions, that's fine, and I am done.

DR. GARCIA: Thank you.

MR. SANTORO: Thank you.

DR. GARCIA: Speaker number 3, please unmute, and you may turn on your webcam. Will speaker number 3 please begin and introduce yourself? Please state your name and any organization you are representing, for the record. You also have five minutes.

DR. CRAWFORD: Thanks, Dr. Garcia. My name is E. David Crawford. I'm a professor of urology and Jack A Vickers director of prostate cancer research at the University of California in San Diego. My career is focused on prostate cancer, particularly advanced prostate cancer. I've had something like 850 peer-reviewed articles published, many of them in prostate cancer, 35 in the New England Journal of Medicine, and Dr. Shore is catching up with me, but I'm going to keep it up. I ran the GU committee of SWOG for 28 years,

and had the opportunity to work with many different drugs and protocols over a period of time.

I am receiving no pay. I was asked about whether this was self from the department and from the company. It's a little bit of everything that's got me here, and this was generated after discussions after GU ASCO and the presentations.

I came with a sort of an open mind. I wrote down three things that I heard in these excellent discussions, and we heard the glass is half empty, half full, and back and forth, and a lot of great discussion. I think it follows on what Mark Twain or Rogers said a long time ago. The problem is, "It ain't what we don't know but what we know that ain't so." And we're focused a lot on the BRCA mutations and what impact that has, and we think that we know that's what works, but maybe it ain't so, and there may be other things.

I think when I give talks on markers, I always talk about these are not pregnancy tests where it's yes or no and they give you some direction, and I think the same thing applies here.

The direction I hear is positive. The other thing is we hear a lot about statistics and p-values. We live by those. I've lived by those in SWOG over the years. We had an MVAC trial we presented at the ASCO meeting plenary session, and that was a positive study, but there was a lot of argument about one versus two-sided p-values, and we wasted many years talking about that. It's currently the gold standard, and we had many more like that.

Finally, what I think about is doing a lot of protocols in my life and looking at things. Nothing will ever be accomplished, and every objection's overcome. In every protocol, there are always objections and things like that. I've lived through those with studies we did in 1989 on adding an anti-androgen to the prostate cancer regimen, and we argued for 15 years about maybe Lupron's a bad drug and an anti-androgen made it look better, and so forth.

It's only recently that now the doublet therapy is being accepted, and now we have triplet therapy. And when you think about it, every cancer

we cure, it's not just one therapy followed by a number 2 or 3, but it's combinations. I think we're there with prostate cancer. We've got a lot of great tools in front of us, the advances that have been made, and a lot of diseases have been small steps. This isn't a huge step, but I agree with my colleague, Rana McKay from San Diego, that this is a step forward. It's something that we heard about. It's reasonably well tolerated. It offers some opportunity to improve care.

My goal, and many of us, is to see that we turn prostate cancer into a chronic disease, and we're seeing that. We just need to take the steps. With that, I will end.

Clarifying Questions to Presenters (continued)

DR. GARCIA: Thank you, Dr. Crawford.

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

Just for the committee, the FDA, and the applicant, it's around 2:48. I think we could actually probably have around 10-15 minutes of time

if we want to actually go back to clarifying questions for the applicant or the FDA, and maybe even within our group in the committee.

We will now take some remaining clarifying questions. Please use the raise-hand icon to indicate that you have a question, and remember to put your hand down after you have asked your question. 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.

As a gentle reminder, 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. Please unmute yourself and turn on your web camera when speaking.

Mr. Mitchell, go ahead.

MR. MITCHELL: Thank you, Dr. Garcia. I would like to reference the FDA slide 20, which is PROpel, and it has the green, and the yellow, and

the pink boxes. Can we get that slide up from the FDA? Thank you.

I've got a two-part question. One is, does AstraZeneca, although they may not like the groupings of the data in this way, agree with what this slide shows in terms of presenting the data in these groupings?

DR. MASSACESI: I will ask Dr. Toms to come and comment on this, and then maybe, Dr. George, if you can comment on the clinical view of this.

MR. MITCHELL: I just want to know, does this slide accurately reflect the data even if you don't like the way the data are grouped?

DR. TOMS: Yes, it does, yes.

MR. MITCHELL: Okay.

So earlier on, there was a discussion about whether, clinically, it's possible to test people to find out if they have the BRCA mutation, and there was a long discussion about the fact that you tried to get some of these people who have undetermined status tested, and it was difficult. So I want to ask both the FDA and AstraZeneca, in

clinical practice, is it possible for us to test people? Because when you look at this slide, the non-BRCA people don't do so well, but the BRCA people do great. And if we could test the undetermined people and find out if they are, in fact, positive, we're going to make sure that we're getting this wonderful drug to the right people, and we're going to get results like we see in the green box for the people who we can determine, through testing in the yellow box, that they have the mutation.

Doesn't that go directly to the question we're being asked to give an answer on? That's both for AstraZeneca and the FDA. Can we test those people and find out if they're positive, and then we'll get that drug to the right people?

DR. MASSACESI: I have the open mic. Dr. George, do you want to comment and share your opinion?

DR. GEORGE: Yes. Dan George, Duke. Thank you for the question. I think one of the things that's really confusing here is the terminology.

The FDA uses this terminology of undetermined population, when in fact those patients that are, quote, "undetermined," are both negative for BRCA by germline and they're negative by BRCA by one somatic test, either the ctDNA or the tumor test.

So these are patients that have two negative BRCA tests. To call them undetermined, in my opinion, is misleading. These are patients that are non-BRCA. Do we know beyond a shadow of a doubt that they're non-BRCA? No. But there's probably a 3 percent chance that that population has a BRCA positive mutation that we didn't detect, and the ability to detect that last 3 percent is probably really difficult to do, even with extra testing, biopsies, and what-have-you? So it's very diminishing return.

To recognize in practice, when we have two negative BRCA tests, a germline and one somatic test, we're going to treat that patient as a negative BRCA patient, as a non-BRCA patient. That's really important for everybody here to understand. These are not undetermined. They're

not as perfectly determined as we'd like. We'd like to have three negative tests, but they have two negative tests, and they are non-BRCA in the vast majority of cases. And in practice, in the real world, that's the population that's probably 90 percent of who we're going to see. So if you exclude the treatment for that population, that 35 percent that you see there, that clinical benefit that you see there is going to be unrealized.

Now is that harm? Possibly. It's dependent on, again, semantics and how you want to consider it, but it's denying patients an opportunity to potentially benefit further from this combination versus abiraterone alone, and I think that's what this is really all about.

DR. MASSACESI: Thank you.

MR. MITCHELL: Can I hear the FDA response to that?

DR. SUZMAN: This is Daniel Suzman [inaudible - audio gaps] -- add some additional comments.

To the question of whether it is possible to gain further clarity on the BRCA status of that 35 percent, I think the answer is likely yes, but in the trial we don't know. Again, the way this trial was conducted was that retrospective testing was done on tissue that was available from predominantly prior small prostate biopsies and some number of radical prostatectomy specimens. We don't know in those patients, if it was known that the tissue testing had failed, whether or not additional biopsies from a lymph node, let's say, could have been performed. Again, we don't have the answer to that question, and we have to rely on the data at hand that was collected.

MR. MITCHELL: I'm not really asking so much about how these people were tested, but is it possible to discern in clinical practice which people in that yellow box actually are positive for BRCA, and to sort them? And I just heard AstraZeneca say, practically speaking, these people are all negative.

DR. SUZMAN: FDA does not regulate the

practice of medicine and how biopsies are conducted in a clinical setting, where we have to rely on the way that the trial was conducted and the way the tumor samples were obtained and tested on PROpel.

DR. KLUETZ: This is Paul Kluetz from FDA. Mr. Mitchell, I think it would be interesting for us to actually hear from the other practicing oncologists that are on the panel to see whether they believe that it is possible that routine care can get to better testing for BRCA. We acknowledge that testing in prostate cancer patients, particularly for tissue, is more challenging than other scenarios, but I would be interested to hear what the other panelists think about that question because I think it's important.

Also, at some point, we would like to move the discussion towards thinking about the magnitude of benefit in rPFS that we're seeing in the non-BRCA group, as defined by AstraZeneca as well as defined by the FDA. Yes, there is an rPFS benefit, but it is lower than any benefit that we've approved drugs in this early-line setting.

So I think that would be an important conversation to have; does the benefit seen in the negatives, of the magnitude that they're seeing, outweigh the risks, which are tolerability, bone marrow suppression, and is that worth treating 85 percent of the population?

So first, maybe we could hear the panel's thoughts on testing, and then maybe we can move a little bit towards looking at risk-benefit considerations across the BRCA negative population.

MR. MITCHELL: That's great. That would be very helpful to me. Thank you, and I'm done, Dr. Garcia.

DR. GARCIA: Thanks, and thanks to the FDA.

I can comment. Obviously, I do prostate cancer for a living. I do agree with Dr. Shore, Dr. Armstrong, and Dr. George as well. Testing in the United States is complex. It may be a deficiency from our providers in a community and in some academic centers to actually remind themselves that everybody gets to be tested for germline and also for somatics. At the end of the day, for

those who actually do a test study, if you will, it is impractical for us to do biopsies in prostate cancer and something that we have all debated for two decades; but in reality, it's impractical to do biopsies.

Now, with regards to how we see the magnitude of the difference, at least for me -- and maybe I'll just put the clinical experts today with AstraZeneca, Dr. George and Dr. Armstrong, on the spot. The data is the data, so I think that we all talk about semantics, and I think many of us heard Dr. George talking about, well, it's just how we interpret the data, but at the end of the day, the data that we have in PROpel is the data that we have in PROpel. The analysis that we have in PROpel is the analysis that we have in PROpel, and how we interpret that data clinically is my interpretation of the data, but it's not the data itself.

So it would be also impossible, in my personal opinion at least, to take these data in a vacuum, and by that I mean, I cannot think of

PROpel alone when I'm thinking as to the role of PARP inhibitors in combination with no hormonal agents for men with metastatic castration-resistant prostate cancer. Obviously, the things that come to mind are PROfound, TRITON-2, and TRITON-3, which I'm going to move to the side for this discussion because they're truly based upon biomarker positivity, whereas BRCA is specifically for rucaparib or olaparib as a single agent, where you BRCA1, BRCA2, ATM, and there are 12 HRR deficiencies.

But I think the bigger question also is that we have TALAPRO and we also have MAGNITUDE, and MAGNITUDE failed to show improvement in outcome in the HRR negative biomarker patient population. So maybe if I can hear from Dr. George or Dr. Armstrong on how they see that heterogeneity outcome. Obviously, we're not going to be able to compare enza-TALAPRO driven approaches against abi driven approaches, but specifically MAGNITUDE, because I think MAGNITUDE puts that question in my mind as to could this be also an agent or a regimen

that can be given through the HRR negative patient population.

DR. MASSACESI: Dr. Garcia, you called them, so Dr. George and Dr. Armstrong will answer this question, and eventually, our scientist, Dr. O'Connor, can explain some molecular -- behind this -- differences among the PARP inhibitors, and also maybe can explain why there are some differences.

Please?

DR. GEORGE: Thank you. Dan George, Duke.

Dr. Garcia, it's a dangerous exercise, as you know, comparing one study to another, but we do it because we have to. We have various treatment options to consider. But in this case, I think the MAGNITUDE study is really fundamentally a very different design than what we did in PROpel or TALAPRO-2. And I say that because it's not an intention-to-treat population. It's really two cohorts. It's a cohort of BRCA-HRR patients and it's a cohort of non-HRR patients.

Specifically, I say that because it's

proportionately much more BRCA-HR patients because that's a separate cohort. So it's not like an intention-to-treat population, where you take everybody and you have the natural percentages represented there.

Secondly, this study design was very, very different. It was done in an add-on fashion. It wasn't started together as two separate cohorts. The second cohort was added when results like Study 8 became available and other studies were started, and it was done with a futility analysis, so it was stopped early. And it was stopped early based on a PSA progression-free survival, which typically happens sooner than rPFS. And with a futility analysis, we don't have a large power like the 600 or so patients you see, almost 700 patients from PROpel, that are non-BRCA, so we lose the ability to differentiate early. In addition, patients were allowed to start their abiraterone up to 3 months before adding their PARP inhibitor, and that's just the practical considerations of how to really do all this genetic testing in real time while you

have to treat your patient with metastatic castration-resistant disease.

Then lastly is the drug. The drug is very different. It's a lower dose, and we see different toxicities, higher toxicity rates despite that lower dose, and we see less efficacy. We see less efficacy in MAGNITUDE in the BRCA positive patients with a hazard ratio of 0.76 than what we see in PROpel in the BRCA mutant patients with a hazard ratio of 0.51.

So we've got big differences across the board between these studies, in its size, its structure, its lead-in, timing of drug, and its endpoint. So I don't think, to me, it really factors into my interpretation of the PROpel data.

DR. KLUETZ: Dr. Garcia, I'm sorry to interrupt you, sir, but I think the question was misinterpreted. I'm not interested in the MAGNITUDE study. I'm interested in the panel's -- not AstraZeneca -- practicing oncologists' view on the magnitude of the rPFS effect seen within the data at hand, for the

application at hand, in the BRCA negative population, because the contention is that we are going to treat all-comers ITT, and that even those non-BRCA patients have benefit, And it's been said in the background package, clinically meaningful benefit. But I think that a 5-month rPFS isn't a slam-dunk for what we would call clinical meaningfulness, particularly in the setting of this toxicity.

So I'd like to hear from the panel how they look at rPFS with no OS in frontline mCRPC with this combination, with the toxicity and tolerability that's been discussed. And I apologize for cutting off Dr. George.

DR. GARCIA: No, no. Thank you.

DR. KLUETZ: I just wanted to make sure the question was correct.

DR. GARCIA: Thank you.

Dr. George, if you want, and just to address the FDA comment, maybe we'll have Dr. Rini and Dr. Madan comment.

Dr. Madan, please go ahead.

DR. MADAN: To also answer Dr. Kluetz's other question, which I think was the first one, which was about testing in the clinic, I'm not a biomarker guy. It's not my research. There are a lot of smart people, including some of which are on this call, who are investigating that. I think we're better at it now than we were 5 years ago. It's a constantly moving target. We have to get more disciplined in doing it.

It's kind of funny because after two decades of striving towards precision medicine, it gets hard to celebrate [indiscernible] in this context, which leads to your second point, which is the benefit in the non-mutated patients is I think a little bit in question, and I think, for me, that's amplified by the fact that the rationale is nice, but it's been purported for a lot of different disease states.

I welcome anyone on the call to tell me because I'm ignorant to this, but is there another example where standard-of-care treatment induces or works synergistically with the PARP inhibitor in

non-mutated patients? I know that we suggested that the radiation synergy is based on this, but that's really an hypothesis more than a fact. In fact, radiation combinations with PARP inhibitors haven't demonstrated anything.

So I think that all bundled together, to answer your question, I think we're getting better at biomarkers, but we're not there yet. I think there is a question about the benefit in the non-mutated patients, and the rationale is part of why I have those questions. Thank you.

DR. GARCIA: Thank you, Ravi.

Dr. Rini?

DR. RINI: I was just going to comment about -- I think the question was, is an rPFS benefit of 5 months without OS benefit of value? I would say as a clinician that treats prostate cancer, it would be. I think there was one analysis maybe in the FDA subset where it was 3 months. I think at that point you're getting down to the scan interval and questions raised that it could be lower than that. I think that's

probably a bare minimum, but if the direct question was about a 5-month rPFS, I do think that's of clinical benefit.

DR. GARCIA: Thanks, Brian.

Dr. Graff?

(No response.)

DR. MADAN: Sorry.

DR. GARCIA: I think you're muted, Dr. Graff.

DR. MADAN: Okay. I just want to also go back to the survival readout for this trial. It's very, very suspect. We have people with known BRCA2 mutations who never got a PARP inhibitor, and they're somehow being put on equal footing with patients who did get a PARP inhibitor. We know from phase 3 trials those patients are going to do worse. I would love survival data that answers the sequencing question. I don't think this trial can ever give us that because of that fundamental flaw.

DR. GARCIA: Thank you.

Dr. Graff, Julie Graff.

DR. GRAFF: Thank you. This is Julie Graff,

medical oncologist, primarily at the VA medical system. I think we're way beyond looking at rPFS when it comes to drug approvals in prostate cancer, given how many effective drugs we have. I think there was an opportunity that was missed here to really do a better job of selecting patients, and therefore kind of forcing us into a position where we're considering some patients where maybe the biomarker status isn't completely understood.

This might be horrible to say -- I don't know -- but the three people talking for AstraZeneca are getting lots of money from pharmaceutical companies each year, and I think that decreases their believability.

DR. GARCIA: Thank you.

So just a comment also to address the FDA, I agree with Dr. Rini. I think that if you look at the sequence of events for someone who's progressing, who may have unknown BRCA or indeterminate BRCA mutation, and if you were not to use the combination of abi and a PARP inhibitor, in this case olaparib, traditionally the sequence for

most would be chemotherapy docetaxel based. The median survival for docetaxel-based chemotherapy in that context is not that great, even though it's historical data from the '90s and 2000.

Having said that, the toxicity profile also comes into question. There are a lot of people, as mentioned earlier, who have many symptomatic disease, some even asymptomatic disease, and justifying putting someone on docetaxel-based chemotherapy, and someone especially without symptoms, is not easy clinically to do. And I would argue that the median improvement with an agent that may have some toxicities that we know, to some extent, how to manage may prove to be clinically beneficial for some.

Mr. Mitchell?

MR. MITCHELL: Thank you. I still want to ask the FDA what AstraZeneca said to me a moment ago, that in fact the people who the FDA refer to as undetermined were, in effect, actually negative because they had two tests that indicated that they were BRCA negative. Why does the FDA use the term

"undetermined" and how could they be determined? I still want to ask, again, is it impractical for me to believe, or to think, that in the course of treating these people, that we could learn whether or not they're BRCA positive, and therefore, clearly, they would be candidates for this drug?

So it's a two-part question. Why does the FDA call them undetermined, and is there a way to determine, in clinical practice -- I heard you say, Dr. Garcia, it's tough to do biopsies, but is there a way in clinical practice to determine their BRCA status, therefore making it clear, based on these data on slide 20 that I keep coming back to, that would indicate they absolutely should get this drug?

FDA, why are they undetermined?

DR. SUZMAN: Yes. This is Daniel Suzman, FDA. I'll start, and I'll see if any of my colleagues want to comment. I believe the definition of undetermined per our definition was based on ctDNA and on tumor tissue testing, which was the testing that was intended to be performed

on all patients.

DR. WEINSTOCK: Hi. It's Chana Weinstock, and I'll add that the majority of the patients in that yellow subgroup, the tumor tissue test was what made their status undetermined. I think there is a lot of uncertainty, and that was borne out when we looked at the results, because if we did look at patients with two negative BRCA tests based on ctDNA and tumor tissue testing, then the results to us look very different. So there was something else going on there, and a lot of it was based on tumor tissue results that were indeterminate or missing, unknown as it were.

DR. KLUETZ: This is Paul Kluetz. So the reality is that ctDNA is a liquid biopsy. It is a blood test, and it's the way that we can get access to this information in an easier way in prostate cancer patients. So with ctDNA negative, then some people would get tumor tissue biopsy, and they might be positive, and those would be BRCA positive patients, but oftentimes that was unable to be obtained; that tissue test was unable to be

obtained, and that would be called indeterminate mainly because we know that the sensitivity of ctDNA isn't as high, and that is a drawback to the current situation with precision oncology in prostate cancer.

DR. FALLAH: Hi. Jaleh Fallah. Can I also add something? As far as I know, we did not receive any patient IDs and detailed information on the patients' germline testing. The information we had was 26 patients had positive germline test results, which were actually the majority of them, except 2 patients were in the BRCA positive subgroup.

MR. MITCHELL: Okay. Is testing, as Dr. Garcia was saying, difficult to determine BRCA status, thereby making it hard to have a determination for all patients?

DR. SUZMAN: Yes. This is Daniel Suzman. I think we acknowledge that many patients may not have an accessible soft tissue for biopsy; some do. But again, we don't know from the way this trial was conducted because the majority of the tumor

tissue samples were archived tissue. So we don't know among patients who had tumor tissue failure, how many of them could have had a re-biopsy or other tissue available that could have been adequately tested for BRCA status.

MR. MITCHELL: Okay. Thank you.

DR. GARCIA: Thank you.

Dr. Conaway?

DR. CONAWAY: Yes. I think I'm asking the same question as Mr. Mitchell was getting at. We've heard a lot of discussion about what was done in the trial in terms of testing and if it can be done, but I guess the question is, will it be done?

Right now, less than half of patients are being tested. In the future, is it accurate to think that less than fewer than the half of patients will be tested, so that fewer than half of the patients for whom this is appropriate will get the therapy? Can there be some discussion, not about the testing in the trial but the clinical care, and whether we have faith that testing will be done at a high enough rate and accurately enough

to identify the patients for whom this therapy would be appropriate?

DR. GARCIA: I think you raise a great question, Dr. Conaway. I think that might be a concern if there's an unrestricted label for the combination, and is precisely that. Why would I have to test if I have access to both agents in an unrestricted manner? So I think that we run the risk of patients who don't need necessarily to undergo testing just because it is approved for all-comers. That is a concern that I have clinically, and unequivocally there is a proportion of patients among those who would not derive benefit at all from therapy.

DR. KLUETZ: Dr. Garcia -- this is Paul Kluetz from the FDA -- I think one of the things that challenged our review is the difference in the situations that we've had before, where we had a biomarker situation where there was a win in the ITT, a win in the biomarker, and it was just complementary information, understanding that some patients would be treated who would not benefit.

When we look at our enrichment guidance, which was discussed a little bit in our slide deck, some of the considerations that we think about as to whether to restrict include the size of the population and the percentage of the population who are biomarker negative. So in this situation, we have a higher risk situation where the biomarker negative population is very large; at least in this trial it was over 85 percent.

The second thing that we thought about, just for clinical context that was a little more challenging, is in other monotherapy situations, where we give the physician and the patient the benefit of the doubt and we don't have the biomarker information, so we treat anyway, in a monotherapy, if it's ineffective, you will know, as we all know as oncologists, in 8 weeks, or a month or two when the scan comes back, that they've progressed, so the exposure to the therapy will be shorter. And in this combination situation, the abiraterone will pick up the efficacy for, as we know from the placebo arm, a long time, well over a

year, even if that PARP inhibitor was completely ineffective.

So the two variables that were a little different in this were, number one, a very large biomarker negative if you're looking at BRCA population, and number two, the inability to see lack of efficacy earlier than we normally would with a precision oncology monotherapy. So I hope that provides some extra context to the challenge.

DR. GARCIA: Thank you. I appreciate that.

DR. PAZDUR: This is Rick Pazdur. One point I'd like to bring up, and this goes to drug regulation, is we should be approving a drug in a population that we know it works in. This intermediate group is a very heterogeneous group, and it's kind of what would be a practice of medicine type of a situation, where people would have a discussion if they did not have the appropriate biopsy information on whether the patient should be re-biopsied, what is the risk of the re-biopsy, et cetera, versus treating a patient for potentially almost a year with this therapy.

So that is kind of a practice of medicine. What we should be looking at is, what is the data in front of us and where does that drug work, so to speak. Whether or not you get another biopsy, that is a patient-doctor discussion, depending upon where the disease is located; could they have another ctDNA test. These are practice of medicine situations when you get into a relatively undefined group.

Remember, the whole purpose of a clinical trial is really to define a homogeneous group of patients, and when you do have a situation where there may be differential outcomes, based on BRCA status or other biomarkers, you would want to stratify and also do separate analysis that would be planned in the statistical plan. This was not done here, so we're guessing on what this heterogeneous middle population is. Nobody knows; let's face it. You could characterize this and do as many sensitivity and exploratory analyses. It is not biologically defined; it's clinically defined, and retrospectively clinically defined.

So when we're doing drug regulation, we should be approving a drug in a population that you know it works in, not that you're guessing it works in. I want to make that clear to the committee here. We can't guess where a drug works. We should have a definition of where it works, and this has been done by other subsequent sponsors in their clinical trials, as was pointed out, in prospectively defining this population.

When we had conversations about coming to ODAC with this group, AstraZeneca representatives said they would not have done this clinical trial this way. So now we're left with a population where we're guessing in this middle group that constitutes a very ill-defined group here. Nobody knows what this group is. It's not biologically defined. It's perhaps clinically defined by practice; how many biopsies one wants to get; where the patients are treated. If they were treated in an academic medical center, would they have, perhaps, a greater propensity to get a second biopsy or their first biopsy? So there's a lack of

clarity of exactly what this population is, and when we do a regulatory decision, we should be approving a drug in a population that we know it works in.

DR. WEINSTOCK: I do want to make the point -- it's Chana Weinstock -- that our issues with the testing strategy used in PROpel are not around the BRCA-mutated subgroup. In that subgroup we define BRCA mutated as positive by either ctDNA or tumor tissue testing, because like I said, this testing strategy is very good at ruling in a mutation, so if there's one test that's positive, we can identify those patients. And for purposes of our analyses, we identified that subgroup using the testing strategy that would presumably be available to everybody, and just one positive mutation result helped define this subgroup.

So I just wanted to make that distinction. The problem comes when you're trying to call a patient BRCA negative, and do that with certainty, and that's where we get into trouble, and that's where the heterogeneity comes in.

DR. PAZDUR: And we also believe that patients should have a right to know whether they're BRCA positive or BRCA negative. They may be making different decisions based on that knowledge, and not having that information and giving a broad indication here really would kind of have a detrimental effect in people actually going ahead and actually re-biopsying people, for example, or getting that information.

So we're kind of at an interface between drug regulation and the practice of medicine, and if this group was better defined, that would be a different situation. But it can't be defined because it reflects a practice of medicine situation, where somebody was treated, et cetera. But I really think that people would want to know, as they do in other diseases, such as ovarian cancer, if you're BRCA positive, you would get this therapy; if you're not, you're not going to get this therapy. What would be the magnitude of benefit that I would get? If I was sitting down with a doctor, my oncologist, I would ask, "Should

we re-biopsy it?" Or if it can't be biopsied, these are the options. These are the extremes here; take your chances, so to speak. But that's a discussion that a patient would have with their physician. That's the practice of medicine, and we do not regulate practice of medicine.

DR. GARCIA: Thank you, Dr. Pazdur.

AstraZeneca?

DR. MASSACESI: Thank you, Dr. Garcia. I would like to call Dr. Armstrong to try to answer all of these train of comments from the agency. Thank you.

DR. ARMSTRONG: Andy Armstrong, Duke University. I think you make great points, and as somebody who practices medicine on a daily basis; follows NCCN guidelines to do germline testing in the vast majority of patients; and tries to get a precision test; even if this was broadly approved, this would not dissuade me from offering precision tests to better inform the risk-benefit discussion in the choice that patients have to see this potential progression-free and overall survival

benefit.

I think we did a very good job of characterizing this yellow group as best as we could by modern practices by offering both a tumor and germline test, and having negativity for both of those groups of patients, where the hazard ratio in that yellow group for rPFS was 0.66. That was a substantial delay in clinical and radiographic progression over time.

DR. MASSACESI: And with regard to the testing, as I stated, the company position is clearly supportive of this. We actually would embrace a complementary diagnostic, even in the case of an open label. This is very [indiscernible] to us.

I think Dr. Shore has a comment to do on a prior comment.

DR. SHORE: Neal Shore, GenesisCare. As a practicing uro-oncologist, I completely agree with Dr. Pazdur that it is all about choice. We want patients to have the choice with their physicians. I certainly do, and this is the conversation I

have. "Are you up? Are you prepared to have a biopsy?" Now, not all patients are prepared and willing to go forward with a biopsy, a repeat biopsy, for a multitude of reasons. So we do the best that we can by getting blood-based liquid biopsy or the ctDNA in a germline. So invariably, that's what occurred in what the FDA is calling the unknown, but we have that in our aggregate population, and we did the best that we can in getting somatic tissue as well.

Dr. Madan said, well, do you have another confirmatory trial where a PARP inhibitor specifically was added to another drug where we saw benefit? And the answer is yes. It's the TALAPRO-2 trial, and it's a phase 3 trial that was just presented; so essentially the exact same rPFS in the intent-to-treat population, given that they had prospective testing, so the same rPFS value.

I just wanted to close by just saying for Dr. Graff's commentary, impugning the panel because there may be honorarium associated with doing consultations, advisory boards, et cetera, I'm not

salaried by any pharma companies, and I've published over 400 papers now, and I work on the U.S. VA Advisory Prostate Cancer Committee. So I think that that was impugning the integrity of the panel and was very unfortunate.

DR. GARCIA: Thank you, Dr. Shore.

DR. MASSACESI: Thank you.

DR. GARCIA: Thank you.

Dr. Madan, do you have a comment?

DR. MADAN: I appreciate Dr. Shore's response. I was looking at something other than prostate cancer. I would actually have the exact same questions for the TALAPRO data in terms of the combination for sequencing, so I'm not sure that's the perfect example or answer there. Thank you.

DR. GARCIA: Thank you.

I see one raised hand, AstraZeneca.

DR. MASSACESI: I think Dr. O'Connor wants to try to answer especially the question that Dr. Madan raised, please.

DR. O'CONNOR: Mark O'Connor, chief scientist in oncology at AstraZeneca. We do think

that this combination works in the ITT population because the thing that those cancers have in common is the androgen receptor. And I know that you asked a question about outside of prostate cancer, and I think in scenarios such as ovarian cancer, where we're using monotherapy, it's clear that you have the benefit in BRCA and in HRRm. However, I think the point here is that we've been able to make that connection between the androgen receptor and its role in DNA repair and the PARP inhibitor, and how they work together, and the combination of a PARP inhibitor plus NHA, leading to more DNA damage.

I think that's what's driving the additional activity, and it's not just random; it's mechanistically based. And I think that's why we see the effect even in the non-BRCA/non-HRRm. So yes, there will be the greatest activity in BRCA, but what we've seen is also the activity extending into the non-BRCA/non-HRRm, and it is biologically relevant, and it is prostate-specific in this case.

DR. MASSACESI: Thank you.

DR. GARCIA: Does the FDA want to comment?

DR. KLUETZ: This is Paul Kluetz. I would just want to reorient to say that rPFS is an endpoint that was accepted for regular approval in frontline prostate cancer. I think OS, we've been looking at very much in the setting of safety and assuring that it's going the right way, and that's not uncommon in many diseases because in earlier lines, we end up using PFS because we know crossover and many other things occur.

But what is different here is that in metastatic, castration-sensitive, and multiple prostate cancer settings, in the metastatic setting, we haven't approved a drug with a magnitude of this kind in the BRCA negative population. So maybe Dr. Suzman can walk through some of the prior approvals just for reference to show what the BRCA negative population would look like compared to what other prior approvals have been in the metastatic setting.

DR. SUZMAN: Sure. This is Daniel Suzman. Could we bring up FDA backup slide 48, please?

I just want to reiterate that in the BRCA negative setting, without demonstrated tumor BRCA mutation that comprises almost 90 percent of the ITT population in PROpel, the hazard ratio for rPFS was 0.77 with a magnitude, again, of 5 months. Again, this would represent a much smaller magnitude of rPFS improvement than we've seen in other drugs approved in the frontline mCRPC setting, specifically abiraterone and enzalutamide, which each had rPFS hazard ratios of substantially less than 0.5 and median rPFS improvements of between 8 to 15 months.

Could we move to slide 49, please? Further, looking in other settings, both in the metastatic castration-sensitive setting and in later line mCRPC settings, we again see rPFS hazard ratios in drugs in which rPFS data was collected well enough to be labeled in the FDA label, hazard ratios of 0.54 at the greatest, but generally of substantially less than we are seeing in the PROpel data for the non-BRCA patients. And again, most of the drugs in this setting were approved based on

OS, so it's only a limited number of drugs in which rPFS at the time of approval was the primary basis for the benefit that was seen.

DR. GARCIA: Thank you.

Dr. Rosko?

DR. ROSKO: Ashley Rosko, Ohio State. I'm listening intently to the discussion, and clearly there are limitations in verifying BRCA status within the rigor of a clinical trial. NOV [ph] is clearly displayed here and will no doubt be amplified in the real-world setting as it is currently. So as I'm listening to the discussion, as a clinician, I'm intent on understanding the consequences of giving a drug to a patient if I do not know the BRCA status.

This brings me back to this pattern of potential overall survival detriment for patients who do not have a BRCA mutation and whether or not the information regarding the subgroup analysis for the final analysis for Study 8, in terms of overall survival, if that information is available to us in terms of the potential adverse events that a

patient could experience, and if it's similar to the PROpel data that we are analyzing here today.

DR. GARCIA: Thank you.

AstraZeneca?

DR. MASSACESI: Dr. Garcia, can we try to answer also the analysis that actually is currently projected because I think we were comparing PROpel to studies that were in the same setting and are very different because they were placebo-controlled studies, and this is not a study against placebo; it's a study against a very active agent that is abiraterone.

My apologies, Dr. Rosko. If you can be patient, we would like to address the comment on that question, and then we will come back to your question. Thank you.

DR. GEORGE: Yes. Dan George, Duke. If I could have CP-3 up? I think the FDA has clarified for us that the purpose of the subgroup analyses is to really look for safety signals or populations that could be harmed. The purpose from an efficacy perspective is to really look at the

intention-to-treat population, so we should really focus on that.

If you recall the slide I showed earlier for the PROpel study, you can see the magnitude here of the rPFS benefit in PROpel and the intention-to-treat population against not a placebo, or prednisone alone, which is not a standard of care in prostate cancer, but against an active competitor, abiraterone and prednisone, and was 8.2 months improvement in the median rPFS. And that's comparable to what we see for an improvement in the median rPFS in the COUGAR study; so similar effect size to what COUGAR-302 had shown for their rPFS.

For OS, I think similarly, we see an improvement in the median overall survival of 7.4 months; now, again, a smaller study and wasn't powered for this, but the effect size is similar, if not greater, than what we saw with COUGAR-302 against prednisone. So there is, I think, a pretty comparable historical perspective to justify the benefits of PROpel in this clinical setting.

DR. PAZDUR: Could I jump in here? We're saying that there is a potential for a detrimental effect on overall survival. We're not saying that this has been statistically proven. We don't have to show that. It is the responsibility of AstraZeneca to show that their drug is safe and effective. That is their responsibility. It is not the responsibility of the FDA to show that it is dangerous, and we have to ask ourselves, given the fact that we have two trials here where there is evidence of potential harm, have they met that obligation here? They have the responsibility, AstraZeneca, to show that.

Here again, in oncology, when we have this situation, we're dealing with one trial here. There are many other therapeutic areas that would, especially for a huge indication such as this, demand two trials to be done to show that we're not having this detriment here. It's not so much what it's being compared to; it's the fact that we are seeing it, and nobody really can explain this, and we're seeing it in two trials here. And here

again, it's the potential for a detriment in overall survival. We have to be mindful of that. And here again, it's very hard for us to put out a drug when we are seeing potentials in harm here, and this was brought out in the FDA presentation.

DR. KLUETZ: Also, just a clarification on the trial design, acknowledging that it's an active control, this is an add-on clinical trial, so abiraterone was present in both arms. So this is not like a head-to-head trial where this would be replacing one drug versus another drug, so we are looking at the magnitude carefully in that it is an add-on design.

DR. MASSACESI: Yes, placebo control.

Dr. Turner, do you want to answer the question of Dr. Rosko on the safety profile of Study 8? It was a specific question.

DR. TURNER: Simon Turner, patient safety, AstraZeneca. If we go to slide up, the specific question was around the safety profile of the combination in Study 8, and whether there's a concern here that could have driven a detriment in

the overall survival data. So I just wanted to show you the grade 5 adverse events from Study 8 on the left and the overall safety analysis set on the right, the non-BRCA, double-negative subgroup, which is the one where there's specific concern about there could potentially be a suggestion of OS detriment.

You see there's only a single fatal outcome from adverse event in that non-BRCA, double-negative subgroup. It seemed very unlikely that it assessed the safety profile that could have been responsible for any potential OS detriment in the double-negative number at subgroup in Study 8.

DR. MASSACESI: And reminding that these analyses for potential detriment in Study 8 was run with 23 patients and 17 events, so the hazard ratio is, of course, with a very, very broad confidence interval. Thank you.

DR. GARCIA: Thank you.

I see a raised hand for the FDA. Does your group have any additional comments?

DR. SUZMAN: No, not at this time.

Questions to the Committee and Discussion

DR. GARCIA: Okay. Thank you. Thank you all.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel.

Dr. Jankowski will now provide the instructions for the voting.

DR. JANKOWSKI: Thank you, Dr. Garcia.

This is She-Chia Jankowski, the DFO. We have one question, which is a voting question. Voting members will use the Zoom platform to submit their vote for this meeting. If you are not a voting member, you will be moved to a breakout room while we conduct the vote. After the chairperson has read the voting question into the record and

all questions and discussion regarding the wording of the voting question are complete, we will announce that voting will begin.

A voting window will appear where you can submit your vote. There will be no discussion during the voting session. You should select the radio button that is the round circular button in the window that corresponds to your vote, yes, no, or abstain. Please note that once you click the submit button, you will not be able to change your vote.

Once all voting members have selected their vote, I will announce that the vote is closed. Please note, there will be a temporary, momentary pause as we tally the vote results and return non-voting members into the meeting room. Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Hereafter, the chairperson will go down the list, and each voting member will state their name and their vote into the record.

Are there any questions about the voting

process before we begin?

(No response.)

DR. JANKOWSKI: Since there are no questions, I will hand it back to you, Dr. Garcia, and we can begin. Thank you.

DR. GARCIA: I'm going to read the voting question.

As FDA reviews the proposed indication for olaparib in combination with abiraterone for initial treatment of metastatic castration-resistant prostate cancer, mCRPC, should the indication be restricted to patients whose tumors have a BRCA mutation? If you feel the combination should not be approved for any indication, please abstain from voting and explain your thinking regarding approvability during the post-voting discussion period.

Are there any questions about the wording of this question?

(No response.)

DR. GARCIA: If there are no further questions or comments concerning the wording of the

question, we will now begin the voting.

DR. JANKOWSKI: We will now move non-voting members and participants to the breakout room.

(Voting.)

DR. JANKOWSKI: Voting has closed and is now complete. The voting results will be displayed, and there are a total of 11 yeses, 1 no, and 1 abstention.

Back to you, Dr. Garcia.

DR. GARCIA: Thank you, Dr. Jankowski.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification for your vote, if you wish to. Please unmute yourself and turn on your web camera when speaking.

We'll start with Dr. Harzstark.

DR. HARZSTARK: I have voted yes. Thank you.

DR. GARCIA: Dr. Liu?

DR. LIU: Hi. This is Chris Liu, and I voted yes. Just some comments, I think the question here is, just simply put, does PROpel

prove that patients with non-BRCA-mutated prostate cancer benefit from olaparib, and I believe the answer is that we don't know, and that's why I voted yes to this question.

To Dr. Garcia's stated point previously, I think that there's a concern about the entire class of PARP inhibitors in an unselected population, and we see that in other diseases, but this is only further supported by the negative results in the BRCA negative population and the only prespecified study conducted thus far in prostate cancer, and that's the MAGNITUDE study.

I honestly believe if the applicant and the GU oncology community are convinced that there's evidence of a meaningful benefit in the biomarker negative cohort, I think that this study would be feasible and could be completed. Thank you.

DR. GARCIA: Thank you.

Dr. Graff?

DR. GRAFF: Julie Graff. I voted yes, for many of the reasons that Dr. Liu stated. Thank you.

DR. GARCIA: Thank you.

Dr. Madan?

DR. MADAN: Yes. This is Ravi Madan, NCI. I abstained. The reason I abstained is the question before the committee today provides a difficult choice to be made based on, really, suboptimal data from a suboptimal study design. In my opinion, this is further complicated by the fact that the fundamental rationale of the combination of abiraterone and olaparib is limited and not completely supported by clinical data.

But it's important to realize that a positive trial that does not represent the decision a provider has in clinic does not necessarily impact clinical practice. When I have a patient with a BRCA mutation, I do not have to choose between PARP inhibitor now with abiraterone or never. That is effectively the question this study asks. In practice, I can sequence PARP inhibitor, delaying the known and well-described toxicity of olaparib.

The data that is required and missing in

today's discussion is really a combination for a sequencing question and, unfortunately, that sequencing question cannot be gleaned from this study because of the lack of a crossover, either design or functionally, rendering any overall survival analysis in this particular study highly suspect.

The assertion of the difficulties of precision medicine when determining mutation status are well taken, but the solution can't be exposing tens of thousands of patients a year without an HRR mutation to a toxicity without clear evidence of benefit. That seems to go against our prime directive of do no harm.

For these reasons, I would not favor the use of abiraterone in the clinic with olaparib in the first-line mCRPC setting based on this data set. I am confident, based on existing data, that patients can benefit from sequencing these agents while deferring toxicity sometimes for years. A 5-month PFS is clinically important, but so is 25 months of exposure to enhance toxicity. The efficacy of

sequencing abiraterone with a PARP inhibitor is well supported by robust phase 3 data, and I await an appropriate study that asks a sequencing question that is the most relevant question to be asked in a clinical scenario here in the United States in 2023. Thank you.

DR. GARCIA: Thank you.

Dr. Rosko?

DR. ROSKO: Ashley Rosko, Ohio State. I voted yes. I think the applicant, as stated here, provided clear benefit of olaparib and abiraterone in patients with the BRCA mutation, but the majority of patients will not carry this mutation. I think many of the team that are here on the call, and the applicant as well, indicated this heterogeneity and the disease pathogenesis, and I think an all-comers indication argues against personalizing therapy for metastatic castration-resistant prostate cancer. I support restrictions to patients with a BRCA mutation. Thank you.

DR. GARCIA: Thank you.

Dr. Vasan?

DR. VASAN: Neal Vasan. I voted yes. BRCA mutation predicting PARP inhibitor sensitivity is a hallmark cancer biomarker, and of course this underpins the whole synthetic lethality paradigm in cancer. So I felt that testing -- if lock of the biomarker still predicts for drug efficacy, which is countered in this fundamental paradigm -- requires a high level of scientific rigor, and I did not feel that this level of rigor was met in the trial, given that it did not prospectively perform BRCA testing or power the study around BRCA status, and this resulted in an equivocation of the benefit in the wild-type population, and this combined with the risk of possible OS detriment informed my vote.

I will say that this whole ODAC discussion I think is a clarion call for new, deeper BRCA companion diagnostics that can fully diagnose the BRCA status of a patient, and also a better understanding for the reasons of this decrement in OS for BRCA wild-type patients across tumor types. I think that these innovations for both academics

and industry colleagues are really critical to realizing the full potential of PARP inhibitors in cancer. Thank you

DR. GARCIA: Thank you.

Mr. Kungel?

MR. KUNGEL: My name is Terry Kungel, and there are four issues that I had when I voted yes. The trial design, it is difficult to understand how patient-driven research could intentionally decide to exclude BRCA or HRR status, not stratified by these biomarkers, and exclude prespecified analyses by biomarker status. The PROpel randomized, phase 3 trial design was inappropriate.

The next question is surrogates. We know in long-term trials, it's important to come up with surrogate measures, but if you look at this PROpel trial, there's very little predictive value in the rPFS in the PROpel. In fact, for the non-BRCA, it was 5 months, 22 versus 17, but the median OS in months is negative, a hazard ratio above 1. rPFS was not predictive for OS in the non-BRCA patients. Because of the high mortality rates with CRPC,

there's little need for a surrogate measure. OS rates are normally determined within 5 years, so why use rPFS, especially when it appears to be misleading?

Prostate cancer is a preference-based medical condition for which there is no best treatment. We are telling prostate cancer patients, you have to figure this all out on your own, and we keep giving them more and more treatment options. The applicant wants to give a new choice for all CRPC patients. There's an interesting TED Talk by Barry Schwartz, Paradox of Choice, where he makes an effective case that "More choices mean more paralysis, more confusion, and more regret." Prostate cancer patients need more treatments that are effective, not more choices.

Olaparib for BRCA-HRR patients is a significant success for patients with these mutations, but the OS for non-BRCA patients has a hazard ratio above 1, and if you look at the Kaplan-Meier curve, it demonstrates little to no effect. And finally, there's significant financial

toxicity in all of this, which has really not been addressed, but it's certainly prevalent in advanced prostate cancer. Thank you.

DR. GARCIA: Thank you.

Dr. Rini?

DR. RINI: Thanks. Brian Rini, Vanderbilt. I voted yes to restrict. This was obviously a difficult subject and I thought a really good discussion around this. I think for me, it really came down to that uncertainty that others have mentioned around that 35 percent of patients in that yellow box that FDA described, because of the way that the trial was done, and it's hard, as I think Dr. Pazdur said, to approve the drug with so much uncertainty in that subset.

I actually think there probably could be mechanistic synergy, or at least additivity, to these drugs together, and then potential additive or synergistic clinical effect in the non-BRCA mutated, of course, but I think the burden of proof is on the sponsor to show that in a well-defined prospective study, and I don't think that happened

here.

DR. GARCIA: Thank you.

Mr. Mitchell?

MR. MITCHELL: Yes. Thank you, Dr. Garcia. I voted yes. FDA's job is to approve drugs if they are safe and effective, and I think that by restricting this drug to patients who are BRCA positive, we ensure that this drug is going to be safe and effective for those who receive it.

DR. GARCIA: Thank you.

Dr. Nieva?

DR. NIEVA: I voted no. I do not think the label in this case should be limited to the BRCA-mutated population. This was a positive clinical trial, designed in conjunction with FDA guidance on the endpoints. The FDA has proposed that there should be a restriction to 11 percent of the patient population, and I don't think this level of restriction is justified. Patients with homologous recombination deficient cancers gain significant benefits from PARP therapy, and this has been seen in multiple clinical trials, and the

subgroup of patients with HRD deficiency had a similar outcome for the primary endpoint, similar to the BRCA-mutated patients. A more reasonable restriction might have been to reduce the indication to HRD deficient tumors.

The FDA's justification for selecting BRCA mutation rather than homologous recombination deficient patients is that there was a lack of survival signal in the HRD group. This is not sufficient justification for the additional restriction, given the known problems in subgroup analysis in the setting and the very large PFS benefit seen in the HRD population. And I worry that the approach used in this application can justify removing any subgroup from an application where that subgroup has an OS curve that crosses 1. FDA seems to be looking at these 0S curves in a vacuum and is ignoring the corroborating evidence that the HRD population would benefit significantly.

With regard to the question around biomarker testing, I think the FDA's position that you are

not BRCA negative unless you're BRCA negative twice with inadequate issue in both cases is also inappropriate. Many hormone refractory prostate cancer patients will have only bone metastasis from which to biopsy, and we know that decalcification of such specimens makes them unreliable. The FDA is asking for the current biomarker testing to provide divine truth on the BRCA status of tumors, and I don't think there's ever going to be enough testing to show that something does not exist.

I do think we need to take Dr. Pazdur's comments to heart that the FDA does not regulate the practice of medicine, but I think not approving the drug in the larger population is doing just that. Patients and physicians understand that this drug provides a great deal more benefit in the BRCA positive or the HRD positive group, and minimal benefit if these tests are not positive, and these risks and benefits can be addressed at the patient and physician level.

I do find it interesting that the COVID deaths on trial affect many of the drugs on which

long-term administration of cytotoxics were given. This issue has been brought to ODAC in the past, and I think the current data is revealing that the pandemic survival curves may not reflect post-pandemic survival signals. I compliment the applicant for having data that clearly showed this, and would suggest to the FDA to recognize that some of the toxicity signals obtained during the COVID era may not reflect future toxicity signals. Thank you.

DR. GARCIA: Thank you.

Jorge Garcia. I voted yes. Similar to previous comments, I think that contrary to Dr. Nieva, I felt that Dr. Pazdur's comments resonated with me. It's the role of the FDA to regulate, not to define our practice and how we define what we do within our exam room with the patient.

I think, just simply, the data, the statistical design of the trial, the outcome of the trial did not prove, convincingly, at least to me, that patients without a BRCA mutation would benefit

from the drug. Perhaps more important than that is the concern that I have with the rPFS improvement, however, the confidence interval for that survival for that patient population is crossing 1.

Lastly, as Dr. Shore and Dr. George mentioned, the practice patterns in North America are pretty odd and somewhat disappointing to me, where a significant proportion of our patients are not getting the treatments that are life-prolonging in the frontline castration-naïve or castration-sensitive space, and certainly not in the castration-resistant metastatic space.

So if this combination was granted an unrestricted label, it would bother me because, precisely, we are not practicing the best way, and we're not treating our patients the optimal way. Just imagine if you have access to an unrestricted indication for this combination; predictably a lot of patients in the community will be getting both agents in an unknown setting with regards to biomarker.

Dr. Conaway?

DR. CONAWAY: Mark Conaway, University of Virginia. I voted yes. Although I'm concerned about the availability and accuracy of genetic testing in the clinical setting, the data seems clear the combination has benefit in the BRCA mutation population, but that benefit is not so clear in the non-BRCA mutation group.

DR. GARCIA: Thank you.

Dr. Bitting?

DR. BITTING: Hi. It's Rhonda Bitting. I voted yes, that the approval should be limited to the BRCA mutations. We spent the last 10-15 years talking about the need for predictive biomarkers for the treatment of prostate cancer, and there's no doubt here that patients with BRCA mutations benefit immensely from this therapy. But rather than accepting the fact that the rest of the patients don't benefit as much, or maybe at all, but treating them anyway, we need to better understand those non-BRCA-mutant patients so that we can develop more appropriate treatment strategies. And until then, we first need to do no

harm. Thanks for a very good discussion today.

DR. GARCIA: Thank you.

If I can summarize how the panel viewed the data and voted, perhaps I'll start with the only vote for no, that the FDA may have been a bit too restricted, based upon the existing data with PARP inhibitors in castration-resistant prostate cancer, and perhaps if the label had been extended to those patients with an HRR deficient tumor, maybe that would have been different.

For the person or the vote for abstain, it does appear that this came out to a suboptimal design and suboptimal results, therefore; and again the question of do we do combination therapy or sequencing, as the existing data right now indicates effectiveness when you sequence no homologous, followed by PARP inhibitors for the right biomarker patient-driven population.

For us who voted yes, I think it became the same. I think we all felt the theme was lack of scientific validity to some extent, or the rigor, I should say, of the study and the inability of the

study, based upon that set of 35 percent of the patient population with uncertainty and whether or not that patient population would really derive a benefit; and the concerns, again, of the heterogeneity in the patient population in that castration-resistant setting, and the potential of exposing patients to unnecessary toxicities for little gain, especially when you look at the overall survival data for that patient population.

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

DR. KLUETZ: No. Thank you.

Adjournment

DR. GARCIA: Alright. On behalf of the entire ODAC committee, the standing members, the guest members, I'd like to thank AstraZeneca, the entire team, and clinical experts from the team for their thoughtful presentations and their thoughtful comments. I appreciate the FDA comments as well, and I certainly appreciate the robust discussion and questions that we have within the committee panel.

With that, it's great to see each other face to face instead of an Adobe platform, so thank you all. Have a great night. We will now adjourn the meeting. Thank you.

(Whereupon, at 4:07 p.m., the meeting was adjourned.)