FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Morning Session

Tuesday, May 20, 2025

8:00 a.m. to 11:47 a.m.

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P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

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

My name is Dr. Neil Vasan, and I will be chairing this meeting. I now call the morning session of day 1 of the May 20-21, 2025 meeting of the Oncologic Drugs Advisory Committee to order. We'll start by going around the table and introducing ourselves by stating our names and affiliations. We will start with the FDA to my left and go around the table.

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

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

DR. GORMLEY: Nicole Gormley, Division Director, DHM II, FDA.

DR. RICHARDSON: Nicholas Richardson, Deputy Director, Division of Hematologic Malignancies II, FDA.

DR. MERINO: Margret Merino, Clinical Team Leader, Division of Hematologic Malignancies II, FDA.

DR. SUNSERI: Nicole Sunseri, Clinical Reviewer, DHM II, FDA.

DR. SEO: Dr. Choueiri, if you could please turn on your camera, unmute, and introduce yourself.

DR. CHOUEIRI: Hi. This is Toni Choueiri. I'm an oncologist at Dana-Farber, member of ODAC. I'm participating virtually, and I'm going to turn the camera off when I'm not speaking or asking a question. Thank you.

DR. SPRATT: Dan Spratt. I'm the Chair of Radiation Oncology at University Hospitals Seidman

Cancer Center at Case Western Reserve University.

DR. SEO: Jessica Seo, Designated Federal Officer, FDA.

DR. VASAN: Neil Vasan, breast oncologist, NYU Langone.

MR. MAJKOWSKI: Paul Majkowski. I'm the patient representative, a 28-year survivor of non-Hodgkin's lymphoma.

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

DR. MADAN: Ravi Madan, medical oncology, National Cancer Institute.

DR. McKEAN: Heidi McKean, community medical oncologist, Avera Cancer Institute, South Dakota.

DR. LIEU: Chris Lieu, GI medical oncologist, University of Colorado.

DR. NOOKA: Ajay Nooka, Director of the Myeloma Program at Emory.

DR. FRENKL: Tara Frenkl, Head of Global Medical and Evidence at Bayer.

DR. VASAN: For topics such as those being discussed at this meeting, there are often a

variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask 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 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. Seo will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. SEO: Thank you, Dr. Vasan.

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

The following information on the status of this committee's compliance with the 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 their 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 discussion of the

supplemental biologics license application, or sBLA, 761309/S-001, for glofitamab, or trade name COLUMVI injection, submitted by Genentech, Incorporated. The proposed indication or use is in combination with gemcitabine and oxaliplatin for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, who are not candidates for autologous stem cell transplant. This is a particular matters meeting during which specific matters related to Genentech's sBLA 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. Tara Frenkl is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Frenkl's role at this meeting is to represent industry in general and not any particular company. Dr. Frenkl is employed by Bayer Pharmaceuticals.

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

Thank you, and I'll return the floor to Dr. Vasan.

DR. VASAN: We will now proceed with FDA opening remarks, starting with Dr. Nicole Gormley.

FDA Opening Remarks - Nicole Gormley

DR. GORMLEY: Good morning. I'm Nicole Gormley, a hematologist and Director of the Division of Hematologic Malignancies II. I'll provide a brief introduction to the issues presented by the glofitamab application. Specifically, in this presentation, I will discuss the top-line STARGLO trial results and share some regulatory considerations pertaining to use of foreign data and applicability of results to a U.S. patient population.

Glofitamab is a bispecific CD20-directed CD3 T-cell engager, which was granted accelerated approval in 2023 for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma after two or more lines of systemic therapy. Approval was based on results from a single-arm trial of 132 patients. The overall response rate was 56 percent with a median duration response of 18.4 months. STARGLO was intended as the confirmatory trial to verify and describe the anticipated clinical benefit.

STARGLO was designed as a randomized trial of glofitamab in combination with gemcitabine and oxaliplatin, GemOx, compared to rituximab in combination with GemOx, in patients with relapsed or refractory diffuse large B-cell lymphoma after at least one prior systemic therapy among patients who were deemed not candidates for autologous stem cell transplant.

Patients were randomized 2 to 1, and the primary endpoint was overall survival, with key secondary endpoints of progression-free survival, complete response rate, and duration of CR. Stratification factors included relapsed versus refractory disease and second- versus third-line treatment.

The trial met the primary endpoint with demonstration of a statistically significant improvement in overall survival, and met the key secondary endpoints of PFS and CR, but not duration of CR. However, upon review of the prespecified trial subgroups of interest, notable differences were observed in OS between the Asian population

and the White population, with similar differences observed in groupings based on region, with poorer outcomes in the North American and European regions. Given the similar findings when assessed by race or region, region will be used throughout the remainder of the presentation.

When examining the KM curve based on region, notable differences were observed when assessing the population based on Asian and non-Asian regions. The non-Asian regions have similar results with GemOx compared to R-GemOx. While there is a striking low performance of R-GemOx in the Asian region, the Asian region demonstrated an OS hazard ratio of 0.39, while non-Asian regions showed a hazard ratio of 1.06. Of note, the hazard ratio in the U.S. was 2.62, but there are challenges interpreting the U.S. result, as there were only 25 patients enrolled from the U.S.

These differential trends were also noted in the progression-free survival, complete response, and overall response rate results. The differential treatment results of the STARGLO trial

will be discussed in greater detail by my colleagues, Drs. Merino and Sunseri, and by the applicant, but I would like to review some of the regulatory considerations regarding foreign data and its applicability to the U.S. patient population.

The regulations set forth in the Code of Federal Regulations, or CFR, govern the agency's use of foreign data to support a marketing application. The CFR states that an application based solely on foreign clinical data may be approved if the foreign data are applicable to the U.S. population and U.S. medical practice, among other criteria. While the regulations apply to applications based solely on foreign clinical data, the principles of ensuring foreign data are applicable to the U.S. population and U.S. medical practice are crucial to evaluation of any application, even if data is based on a global trial.

Drug development is often conducted globally, and trials must be designed and conducted

to satisfy multiple regulatory requirements. This can be challenging due to varying statutory requirements and different medical practice standards. Historically, Asian countries have had limited participation in global trials used to support registration. To address this, some Asian regulatory authorities required bridging studies to extrapolate data from the broader, more heterogeneous population to their more homogeneous population.

More recently, we've seen applications submitted to the FDA for review based on trials with data solely from China or with large enrollment from Asia. Historically, U.S. patients have represented 20 percent of the participants enrolled in oncology registrational trials submitted to the U.S. FDA. By comparison, in STARGLO, U.S. patients comprised only 9 percent of patients, and those enrolled in China approximately 30 percent, while Asia as a whole comprised 48 percent of the trial population.

When considering these results, it's

important to keep in mind the demographic makeup of the trial. With 48 percent of the enrollment occurring in Asian countries, 50 percent of the population was Asian, 42 percent were Caucasian, there was 1 percent African American, and no American Indian or Native Hawaiian Pacific Islander representation. There was 6 percent Hispanic ethnicity. As a result, we have limited information on the population representative of those with the disease in the U.S.

FDA and Congress have undertaken several efforts to address the need for U.S. representation in clinical trials used to support approval. The first I'll mention is the Food and Drug Omnibus Reform Act of 2022. This legislation passed by Congress required that sponsors submit a diversity action plan for any phase 3 or pivotal trial. The Diversity Action Plan should specify enrollment goals based on age, sex, race, and ethnicity. The purpose of this legislation was to ensure that the data supporting marketing applications is reflective of the population that would receive the

product in the U.S. if it were approved.

Additionally, the FDA has published draft guidance on multiregional clinical trials to aid sponsors who are planning to conduct global clinical development. A multiregional trial is defined as a trial conducted in multiple countries, geographical, or regulatory regions. There are many strengths associated with use of multiregional clinical trials, some of which are listed on the slide. And although the guidance was published in 2024, it builds on principles outlined in the ICH E5 and E17 guidances.

The draft guidance states that sponsors planning a multiregional clinical trial intended to support approval of an oncologic drug should plan to enroll a sufficient number of U.S. participants in the trial to help ensure that the evidence generated supports a robust assessment of the safety and effectiveness of the drug in U.S. patients with the disease and in the context of U.S. standard of practice and treatments.

As stated earlier, the data used to support

an application must be applicable to the U.S. patient population and the U.S. practice of medicine. ICH E5 guidance outlines principles that can be assessed to determine the acceptability of foreign clinical data. There are intrinsic and extrinsic factors which may be associated with treatment efficacy and safety. Intrinsic factors are those that help define and identify a subpopulation, and examples include genetic polymorphism, age, and gender, among others, while extrinsic factors are those associated with the environment and culture in which a person resides; examples include medical practice, diet, and environmental exposures, among others.

In addition to an assessment of the intrinsic and extrinsic factors that can impact study outcomes, the multiregional clinical trials guidance recommends that the following factors be considered when assessing the adequacy of a global trial: patient-related factors such as the genetic ancestral background or exposure to risk factors; disease-related factors such as prevalence of

disease type or frequency of drivers of oncogenesis; healthcare factors such as access to care, screening practices, and availability of cancer treatments, which may impact prior therapies and subsequent therapies trial participants might receive; and lastly, social cultural factors such as diets and beliefs.

Specifically, as it relates to the STARGLO trial, there are many of these factors which suggest differences between the Asian subpopulation and those enrolled in the U.S. and Europe. These differences will be discussed further by my colleague, Dr. Sunseri, but all of these differences could have played a contributing role in the differential outcomes that were observed in the trial, and limit our ability to have confidence these results are applicable to a U.S. patient population.

Lastly, I'd like to briefly discuss the topic of subgroups. It is worth noting that subgroup results must be interpreted with caution; however, they provide valuable information about

the consistency of the benefit-risk profile across important populations. A consistent benefit-risk assessment across subgroups provides assurances that the treatment benefit observed applies to the entire population studied.

In STARGLO, region was a prespecified subgroup for analysis, and the size of the Asian subgroup represents approximately half the population; so it is a large subpopulation that allows for more confidence in the interpretation of the results.

I'd like to briefly review the evidentiary criteria for approval. For safety, there must be sufficient information to determine that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling. For effectiveness, there must be substantial evidence of effectiveness based on adequate and well-controlled investigations that allow for the conclusion that the drug will have the effect it is represented to have in the proposed labeling.

Historically, there was a requirement for

two adequate and well-controlled trials to establish effectiveness. In oncology, replication was not always feasible, and so there's often been reliance on one adequate and well-controlled trial with confirmatory evidence. But when one trial is used, the trial should demonstrate a clinically meaningful effect of sufficient magnitude and robustness, with demonstration of internal consistency such that a second trial is not warranted.

FDA is not seeking the advice of the committee as to whether STARGLO should be used to convert the accelerated approval of glofitamab to traditional approval; rather, we are asking the committee to discuss if the results of the STARGLO trial are applicable to a U.S. patient population. We would like for the committee to discuss how the differential results observed in the Asian and non-Asian regions impact the overall interpretation of the STARGLO trial results and the generalizability of the STARGLO results to a U.S. patient population.

Thank you very much for your attention.

FDA Opening Remarks - Margret Merino

DR. MERINO: Good morning. My name is Margret Marino, and I'm a hematologist-oncologist and the Cross Disciplinary Team Lead for this application. To expand on Dr. Gormley's opening remarks, I will provide a discussion of the treatment landscape for patients with relapsed or refractory large B-cell lymphoma, the STARGLO trial design and conduct, and highlight the inconsistent treatment results observed across endpoints between the Asian and the non-Asian regional subgroups.

There were key differences identified among intrinsic and extrinsic factors, and taken together, these issues raise concern whether the STARGLO trial results are generalizable and applicable to a U.S. patient population.

Diffuse large B-cell lymphoma, not otherwise specified, or DLBCL, NOS, is a subtype of a larger category of large B-cell lymphoma. Large B-cell lymphomas are considered aggressive, although curable, and are the most common type of

non-Hodgkin's lymphoma.

The classification and the treatment landscape of large B-cell lymphoma is complex and has evolved over the recent years. Large B-cell lymphoma subtypes are based on histopathology and further categorized based on molecular testing. Poor prognostic factors have been identified based on age, ECOG performance score, and advanced disease status. Other poor prognostic factors include the presence of genetic abnormalities involving MYC, BCL2, BCL6, and the activated B cell, ABC, cell of origin subtype.

Patients with newly diagnosed diffuse large B-cell lymphoma are treated with curative intent with chemoimmunotherapy, either R-CHOP or a similar regimen, or polatuzumab vedotin plus R-CHP. Treatment is limited to 6 to 8 cycles, and results and cure for about 60 percent of patients.

For the 40 percent of patients who are not cured with initial therapy, an important consideration is whether the patient is a candidate for CAR T-cell therapy or salvage therapy with an

autologous stem cell transplant. For those able to receive CAR T therapy, up to 20 percent may achieve cure. For those that pursue transplant, there are important eligibility considerations such as chemosensitive disease, age, and the presence of other comorbidities. Overall, transplant can lead to cure in 10 to 20 percent of patients.

For patients not eligible for CAR T or transplant, the available therapies are shown in the red box on this slide. For this population, there is no preferred standard of care treatment regimen, and patients may receive one of several treatments, including chemo immunotherapy or targeted therapies, either alone or in combination.

This table includes the FDA-approved and standard available regimens for patients with relapsed/refractory large B-cell lymphoma. This treatment landscape is rapidly evolving, and there are a number of novel agents available such as the T-cell engagers, CAR T-cell therapy, and antibody drug conjugates, which have improved efficacy in this population. However, standard

chemoimmunotherapy regimens remain options for patient, including R-GemOx, which was the comparator arm for the STARGLO trial.

Glofitamab is a CD20-directed T-cell engager with established activity in patients with relapsed or refractory large B-cell lymphoma, which was granted accelerated approval in June of 2023. Important risks include cytokine release syndrome and infections. To mitigate cytokine release syndrome, obinutuzumab, a CD20-directed antibody, is administered one week prior to glofitamab, along with the glofitamab step-up regimen.

The STARGLO trial was intended to serve as the confirmatory trial for glofitamab. Eligible patients were those with relapsed or refractory diffuse large B-cell lymphoma who are not eligible for transplant. A substitution design was used with glofitamab added to a GemOx backbone compared to a rituximab GemOx control arm, with a primary endpoint of overall survival.

The STARGLO trial met the primary endpoint of OS at an interim analysis with a hazard ratio of

0.59, along with the key secondary endpoints of progression-free survival and complete response rate. At this interim analysis, however, inconsistent treatment results were observed between racial and regional subgroups. This is shown in the Kaplan-Meier curve displaying overall survival results by region.

The discordant results between the Asian region and the non-Asian region is notable. Additionally, it's important to highlight the low performance of the control arm in the Asian region. On the bottom row of the table on the right, the median duration of follow-up for overall survival is shown, with 14.6 months in the Asian region compared to 8.7 months in the non-Asian region.

At the time of the interim analysis, the applicant hypothesized that the differential treatment effect observed between the regions was related to the shorter follow-up time and, hence, a lower number of OS events in the non-Asian region. This histogram shows enrollment over time by region, demonstrating a lag of enrollment in the

U.S. and Europe in the STARGLO trial.

The applicant also assessed that COVID-19-related events may have contributed to the inconsistent trend, and that additional follow-up would likely address the inconsistencies observed. Based on this reasoning, the applicant proposed nine additional months of follow-up and a subsequent analysis.

With an additional follow-up of approximately 11 months, the inconsistent treatment effects in overall survival persisted. While a positive result was observed in the ITT analysis with a hazard ratio of 0.62, the inconsistent results between the regions persisted with similar discordant treatment effects observed for patients treated in the Asian region, with a hazard ratio of 0.39, compared to the non-Asian region, with a hazard ratio of 1.06.

With the updated analysis showing persistence of the inconsistent treatment results despite additional follow-up, the applicant now proposes that the inconsistent results may be due

to differences in new anti-lymphoma therapy or NALT. Additionally, they point out the limitations of subgroups and imbalances in disease characteristics in the U.S. patients. I will discuss NALT in the next slide. While there are some limitations of subgroups, they are important to evaluate to assess the consistency of the treatment effect in clinical trials. Lastly, we note the U.S. enrollment of only 25 patients, limiting further evaluation of this population.

I'd like to briefly discuss NALT as it relates to the clinical trial endpoints as depicted in this figure. NALT is therapy received after discontinuing study treatment, either for disease progression or for other reasons such as toxicity. Overall survival as an endpoint incorporates the receipt of NALT, and the overall survival results could be impacted by NALT depending on the type and availability of subsequent anti-lymphoma therapies. Importantly, NALT does not generally impact other endpoints such as progression-free survival, or response-based endpoints such as overall response

rate and complete response rate.

Importantly, in the STARGLO trial, the inconsistent treatment effects by region was observed across the secondary endpoints of PFS and overall and complete response rate, which is, again, not explained by NALT. As shown in the table, a general pattern is observed where there is a large treatment effect demonstrated in patients treated in the Asian region, with an OS hazard ratio of 0.39, a PFS hazard ratio of 0.25, and a difference in overall response rate and complete response rate of 46 percent and 44 percent, respectively. This is in direct contrast to the minimal or notably decreased effect observed in patients treated in non-Asian regions, with an OS hazard ratio of 1.06, a PFS hazard ratio of 0.81, and a difference in the overall response rate and complete response rate of 9 percent and 22 percent, respectively.

The FDA considers these findings relevant and important in the interpretation of the STARGLO trial results. If the OS results in the non-Asian

region were considered true, this could indicate a signal for harm for patients in non-Asian regions.

In order to further evaluate potential reasons for the inconsistent results between regional subgroups, the FDA evaluated the STARGLO data for differences in patient, disease, and healthcare system-related factors between the Asian region and the non-Asian region. As you will hear in the FDA presentation, regional differences in relevant patient characteristics such as age, race, and transplant eligibility, disease characteristics such as early relapse and cell of origin, and healthcare system factors such as the timing of assessments and the types of NALT received were identified. These will all be covered in detail in the upcoming FDA presentation.

The last topic I will discuss is applicability of results to the U.S. patient population. First, it's important to reiterate that the low U.S. enrollment is a significant limitation. There were only 25 patients enrolled from the U.S., representing 9 percent of the total

trial population. This is in contrast to the relatively high representation of patients enrolled in Asian countries at 48 percent, including 34 percent of patients from China and Taiwan. The protocol specified that a minimum number of patients, 80, would be enrolled from China either in the main study population or as an extension cohort. There was no such minimum enrollment requirement in the protocol for other countries or regions.

Additionally, the comparator arm of R-GemOx has implications as it relates to the applicability to the U.S. patient population. Although R-GemOx is one of the several chemoimmunotherapy options for patients with relapsed or refractory large B-cell lymphoma, its use in the U.S. is limited and generally reserved for patients who are unable to tolerate more intensive therapies. Furthermore, when it is used, it is often administered on a more frequent schedule, at every 2 weeks in this aggressive lymphoma setting, whereas in the STARGLO trial, it was administered every 3 weeks.

In summary, in the STARGLO trial, a differential treatment effect was observed between patients treated in Asian versus non-Asian regions across multiple endpoints, which raises concerns about the robustness of the study results. The FDA identified differences in patient- and disease-related factors, as well as healthcare system differences that may have contributed to the inconsistent treatment results. These factors, in addition to the low U.S. enrollment, calls into question whether the STARGLO results are applicable and generalizable to a U.S. patient population.

We are asking the committee to discuss how the differential results observed in the Asian and non-Asian regions impact the overall interpretation of the STARGLO trial results and the generalizability to a U.S. patient population. For the voting question, we are asking, are the STARGLO population and trial results applicable to the proposed U.S. patient population. Thank you for your attention.

DR. VASAN: Thank you Dr. Gormley and

Dr. Merino.

Both the 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 participants, including industry's non-employee presenters, to advise the committee of any financial relationships that they may have with industry, such as consulting fees, travel expenses, honoraria, and interest in a sponsor, including equity interests and those based upon the outcome of the meeting.

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

We will now proceed with the presentations from Genentech.

Applicant Presentation - Charles Fuchs

DR. FUCHS: Good morning. I'm Dr. Charles Fuchs, Senior Vice President and Global Head of Oncology and Hematology Product Development at Genentech at Roche. I want to thank Dr. Vasan, the ODAC members, Dr. Pazdur, Dr. Gormley, and the FDA staff for the opportunity to discuss our supplemental biologics license application for glofitamab in combination with gemcitabine and oxaliplatin in the global STARGLO trial.

STARGLO is the first randomized, phase 3 study to meet the primary endpoint of improving overall survival in transplant-ineligible, relapsed/refractory diffuse large B-cell lymphoma, addressing a critical unmet need for U.S. patients.

My background is as a medical oncologist. I previously worked at the Dana-Farber Cancer Institute and subsequently served as Director of the Yale Cancer Center. In 2021, I had the privilege of joining Genentech and Roche to lead

oncology and hematology drug development. I'm joined today by several colleagues. I want to call out the external members of our respondents, Dr. Jeremy Abramson, Dr. Krish Patel, and Dr. Haifaa Abdulhaq. The other members, my colleagues at Genentech and Roche, will introduce themselves during the presentations, as well as the Q&A.

Despite improvements in first-line treatment of DLBCL, 40 percent of patients do not respond or progress following first-line therapy. CAR T therapy represents an important therapeutic advance, but only 25 percent of relapsed/refractory patients in the U.S. are able to receive cellular therapy. For the remaining 75 percent, treatment is principally limited to cytotoxic chemotherapy with a median overall survival of 6 to 12 months, reflecting an urgent need for more effective therapeutic options.

As you heard, glofitamab is a novel CD20/CD3 bispecific that brings together the activated T cell to the malignant CD20 expressing B cell, thereby resulting in potent lysis and meaningful

tumor regression of DLBCL. In contrast to cellular therapy, glofitamab is immediately available off the shelf and avoids the complexities and treatment delays associated with cellular therapy.

Prior to STARGLO, the therapeutic impact of glofitamab was first appreciated from the initial monotherapy study in heavily pretreated, highly refractory, third-line plus DLBCL patients. In this setting, glofitamab monotherapy delivered an unprecedented 40 percent complete response rate with a similar benefit among patients who had progressed on prior CAR T therapy. These responses were highly durable, with a median duration of complete response of 30 months.

Relevant to today's discussion on subgroups and applicability, in this global trial, there were no regional or racial differences in the pharmacokinetic properties, efficacy, or safety for glofitamab.

Based on these exciting results, glofitamab monotherapy received FDA accelerated approval in June 2023 and was also approved in over

60 countries around the globe. Today, more than 6,000 patients have received the treatment worldwide, including 2,000 patients in the U.S. Hereto, real-world evidence across regions of the world supports a consistent efficacy and safety profile for glofitamab across race and region.

At the time of FDA accelerated approval, as you heard, confirmation of clinical benefit was to be demonstrated by the STARGLO trial, expanding availability of glofitamab into the second-line setting in combination with chemotherapy.

Initiated in 2020, in the start of the global pandemic, STARGLO was designed to assess the impact of glofitamab in combination with GemOx on overall survival in a global population, delivering a 41 percent reduction in the risk of death and a 63 percent reduction in the risk of disease progression. These results are both statistically significant and clinically meaningful. Moreover, the results confirm the clinical benefit of glofitamab.

As noted by the FDA, within exploratory

subgroup analyses across 26 covariates and 77 subgroups, hazard ratios greater than 1 were observed in the subgroups of race and region of enrollment, though with wide confidence intervals. It should be noted that STARGLO was not designed or powered to detect differences in treatment effect in exploratory subgroups.

Our colleagues at the FDA have highlighted differences within the Asian subgroup, suggesting that such differences impacted results in Asia. STARGLO was a well-conducted study with highly experienced Asian centers that previously participated in successful global registration trials. As you'll hear today, we conducted a thorough assessment to better understand the subgroup analyses, and along with the FDA understand these results.

First, a multivariable model of the intention-to-treat population that included all the factors cited by the FDA that we'll hear again shortly, patients treated with Glofit-GemOx continued to experience a 41 percent improvement in

overall survival when compared to R-GemOx. Second, regardless of the differences in Asia cited by FDA, the R-GemOx control arm delivered a median overall survival of 8.2 months in Asia, well within the expected range of comparable and contemporaneous cohorts.

In stark contrast, in the subgroup of North America, Europe, and Australia, or non-Asia, R-GemOx was associated with the median overall survival of 27.8 months. This unprecedented performance of the control arm in non-Asia highlights why exploratory subgroups must be viewed cautiously, and it explains the attenuated hazard ratio observed in the subgroup of North America, Europe, and Australia. My colleagues will share additional analyses on the North American, European, and Australian subgroup.

Third and most important, with respect to the intervention arm, Glofit-GemOx, that regimen delivered an overall survival, which was absolutely consistent across North America, Europe, Australia, and Asia, highlighting a consistent benefit of

Glofit-GemOx on overall survival for all patients and emphasizing the applicability of these data to patients in the United States. Based on the analyses that my colleagues will also share, we respectfully submit that the factors in Asia cited by our FDA colleagues did not influence the STARGLO results.

With that introduction, this is our agenda for our presentation. I'll now turn to Dr. Abramson to discuss the DLBCL landscape and the unmet need for patients.

Dr. Abramson?

Applicant Presentation - Jeremy Abramson

DR. ABRAMSON: Good morning. I'm Jeremy Abramson. I'm the Director of the Lymphoma Program at the Massachusetts General Hospital and a Professor of Medicine at Harvard Medical School, and it's my privilege to be with you today to discuss the treatment landscape and unmet medical needs within diffuse large B-cell lymphoma. These are my disclosures, which include consulting from Genentech-Roche, the sponsor.

Diffuse large B-cell lymphoma is the most common lymphoma in the United States and worldwide, accounting for approximately 19,000 new cases every year in the United States and nearly 6,000 deaths. Most patients are older with a median age in the late 60s and require urgent therapy due to the rapidly progressive, aggressive nature of DLBCL.

Importantly, DLBCL is a global disease with similar patient characteristics, management strategies, and outcomes worldwide, and this is reflected in consistent treatment guidelines across the United States, Europe, Asia, and Australia. The goal in treating both frontline and relapsed DLBCL is cure. You've heard that approximately 60 percent of patients with DLBCL will be cured with frontline therapy today, which means that 40 percent of patients will not be, and most of those patients will die of their disease due to lack of availability or access to highly effective therapies today.

Among patients being failed by frontline chemoimmunotherapy, a large proportion have primary

refractory disease, defined as lack of achieving remission or progression within 6 months of frontline chemoimmunotherapy, which constitutes an extremely high-risk population with extremely low response rates and poor overall survival with conventional therapies.

Treatment decisions guiding diffuse large B-cell lymphoma management are informed by response to second-line therapy, and not achieving a complete response to second-line therapy is considered a treatment failure. I want to emphasize this because this is somewhat different from our solid tumor management colleagues, where less than a CR is considered refractory disease and treatment failure, and any patient with less than a CR or progressive disease is considered for a new anti-lymphoma therapy or not. And given the application of NALT for treatment-failure patients with less than a CR, the application of NALT in that population directly impacts progression-free survival.

I will also emphasize that the majority of

patients with relapsed DLBCL today fit into that great treatment failure box, which means that there is a significant unmet medical need for highly effective therapies in the second-line setting.

If we consider the overall treatment population with relapsed and refractory DLBCL after frontline therapy, you will see that only a minority of patients will be candidates for curative intent therapy with either CAR T cells or autologous stem cell transplant, whereas the majority of patients will be treated with non-curative intent options.

There are numerous reasons why patients might not be considered for curative intent therapies. These include advanced age and medical comorbidities, as well as refusal of stem cell transplantation due to the high risk associated with excessive toxicities, the impaired impact of those toxicities on quality of life, and the intense logistics associated with transplantation.

Additionally, significant barriers to access exist for CAR T-cell therapy, including rapid

disease kinetics of relapsed DLBCL, which often do not afford the 6 to 8 weeks minimum required to undergo the CAR T-cell process, as well as geographic and socioeconomic barriers. Since both CAR T cells and autotransplant are only offered at highly specialized centers in the United States, accessing these therapies will often require travel, sometimes for many hours, and relocation of patients and their families to those treating centers to undergo that therapy.

Such logistical barriers are often prohibitive, or unacceptable, or unaffordable to many patients in the United States today. As such, for the majority of patients with relapsed DLBCL today, only limited effective treatment options are available. And you heard from the FDA that there is no single standard of care and that numerous options are available for second-line management. But I will highlight that none of those options induce a complete remission in the majority of patients, and all of those options are associated with disappointingly brief progression-free and

overall survival.

You also heard from the FDA about regional variation in cell of origin with DLBCL, but I wish to emphasize that cell of origin has zero impact, no impact whatsoever, on prognosis or selection of second-line therapy in patients with diffuse large B-cell lymphoma.

Let's look at the distribution of second-line therapies in a real-world population of over 2500 patients receiving second-line treatment for DLBCL. These data are derived from claims data from private and Medicare Advantage programs with a median age similar to that of the STARGLO trial. What you can see is that CAR T-cell therapy and autologous transplant are offered in only 7 and 5 percent of these patients, respectively, and this is in 2024. This means that 88 percent of patients are offered non-curative intent therapy with limited efficacy. And despite the availability of numerous options available, the majority of patients in the United States are treated with chemoimmunotherapy.

R-GemOx is an acceptable and oft-used option for second-line, non-transplant eligible patients, particularly in community-based practices, where the majority of lymphoma care in the United States is provided. R-GemOx is also included as a standard treatment recommendation for this population in treatment guidelines governing the United States, Europe, Asia, and Australia, making this a relevant comparator in the STARGLO population as a standard of care.

To summarize, there continues to be an urgent need for new treatments for relapsed/refractory DLBCL, especially for second-line patients who are considered ineligible for stem cell transplant or lack access to CAR T-cell therapy for whom the treatment options available have limited efficacy.

There is no doubt that modern immunotherapy techniques, including CAR T cells and bispecific antibodies, have transformed the treatment landscape for DLBCL, but as you've seen, CAR T cells are only accessible to a minority of patients

with relapsed DLBCL in the United States today, and bispecific antibodies are only approved in the third-line or later setting, and therefore inaccessible to patients in need in the second line.

As you will hear today, the randomized STARGLO trial shows that glofitamab in combination with gemcitabine and oxaliplatin induces complete remissions in the majority of patients with second-line, non-transplant-eligible DLBCL, and this is associated with substantial improvement in progression-free, event-free, and overall survival.

The STARGLO trial therefore demonstrates that glofitamab-GemOx fills an unmet medical need and provides, for the first time, an active, off-the-shelf immunotherapy option for patients with second-line, non-transplant eligible disease without access or eligibility for CAR T cells, thus holding the promise to provide deep and durable remissions, and ultimately improve cures in this population, hopefully.

With that, I'll thank you very much, and

I'll turn the floor over to Dr. Michelle Boyer to review the details of the STARGLO trial.

Applicant Presentation - Michelle Boyer

DR. BOYER: Thank you, Dr. Abramson.

To address the unmet medical need and transplant-ineligible relapsed/refractory DLBCL patients, we designed and conducted the phase 3 STARGLO study. Today, I'm going to walk you through this data. My name is Michelle Boyer, and I am the Global Head for Lymphoma and CLL Clinical Development at Genentech.

The STARGLO study is an ongoing randomized, open-label, phase 3 clinical trial, evaluating the combination of glofitamab with gemcitabine plus oxaliplatin, compared to rituximab plus gemcitabine and oxaliplatin, in transplant-ineligible patients with relapsed or refractory DLBCL. This was designed as a multiregional clinical trial, enrolling 274 patients globally. Patients were randomized 2 to 1 based on key factors with the strongest evidence of clinical relevance and known to impact outcomes in relapsed/refractory DLBCL.

These are refractory status and number of prior lines of therapy.

In terms of treatment, 183 patients were assigned to the Glofit-GemOx arm and received 8 cycles of glofitamab in combination with GemOx, then up to four additional cycles of glofitamab monotherapy for a total of 12 cycles. Ninety-one patients were assigned to the R-GemOx arm and received up to 8 cycles of Rituximab-GemOx.

The primary endpoint of the study is overall survival with the study powered to detect a meaningful difference using a two-sided alpha. To control for multiplicity, a hierarchical testing strategy was applied to the key secondary endpoints: progression-free survival assessed by an independent review committee, best complete response rate, and duration of complete response. Each test is sequentially at a predefined significance level. An interim analysis was performed at approximately 70 percent of the overall survival events.

STARGLO was a well-conducted, multiregional

trial spanning 4 continents and 13 countries. There were 10 sites in North America, 29 sites in Europe, and 23 sites in Asia Pacific. The U.S. had the highest number of sites per country; however, delayed site activations in North America due to COVID-19 led to lower than anticipated enrollment there. Despite this, STARGLO successively enrolled a diverse global population, highlighting the strength of its design and the commitment of the participating investigators.

Turning to the patients enrolled in this study, the demographics and baseline characteristics reflect a typical group of relapsed or refractory DLBCL patients who were ineligible for transplant. The two treatment arms were well balanced, approximately 60 percent were treated in the second line, and over half were refractory to their last therapy. Over 50 percent had primary refractory disease, defined as those who do not respond to or relapse within 6 months of their first-line therapy. These are hard-to-treat patients known to have the poorest clinical

outcomes, making this a particularly high-risk study population. Enrollment was highest in Asia Pacific, followed by Europe, with 25 patients enrolled in North America.

I want to take a moment here to walk you through this data because understanding how transplant eligibility was defined in this study is critical to interpretation of the STARGLO results. This table summarizes the reason patients in the STARGLO ITT population were considered ineligible for transplant.

Globally, transplant is standard of care only in the second-line setting. In STARGLO, 37 percent of patients were in the third line or beyond, automatically making them transplant ineligible. Among the patients in second line, the most common reasons for transplant ineligibility were advanced age followed by comorbidities. In 29 patients, which is 10.6 percent of the overall study population, the reason was patient refusal.

Importantly, all centers in the study were equipped to offer transplant. In cases of refusal,

this reflects an informed shared decision-making process between the patient and their physician, balancing risks, benefits, and patient preference. This is a valid and globally recognized reason for ineligibility and mirrors real-world clinical practices, where patient autonomy plays a central role.

Having established who was enrolled in the study, we'll now move to the efficacy results.

STARGLO met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in overall survival. At the interim analysis, with a median follow-up with 11.3 months, a hazard ratio of 0.59 was observed, corresponding to a 41 percent reduction in the risk of death versus R-GemOx, with a statistically significant p-value of 0.011. Importantly, this is the first phase 3 study to demonstrate an overall survival benefit in patients with relapsed/refractory DLBCL who are ineligible for transplant, a major milestone for this high-risk population that is predominantly primary

refractory with limited treatment options.

Given the strength of the overall survival benefit, the independent data monitoring committee recommended full analysis of the study, and consequently, the interim analysis became the primary analysis. At the primary analysis, some patients were still on treatment. To ensure all patients completed therapy and to allow for adequate follow-up in all regions, specifically Europe and North America, an updated analysis was conducted with 11 additional months of follow-up.

The updated overall survival data continued to demonstrate a durable clinical benefit with glofitamab plus GemOx. The median overall survival was 25.5 months, nearly double that observed with R-GemOx alone, where the median overall survival was 12.9 months. Recognizing the need for longer follow-up, we observed a plateauing of the survival curve in the glofitamab-GemOx arm, suggesting that a meaningful proportion of patients are achieving long-term survival.

The substantial overall survival benefit was

further supported by a consistent clinically meaningful and statistically significant improvement in progression-free survival. At the primary analysis, glofitamab-GemOx reduced the risk of disease progression or death by 63 percent. With longer follow-up, median PFS was 13.8 months with Glofit-GemOx versus just 3.6 months with R-GemOx alone. The sustained curve separation and 4-fold PFS benefit underscores the durability of response and extended time without relapse.

I want to now orientate you to data at the bottom right of the slide to highlight the importance of this point. We observed a 93 percent concordance between the investigator and independent review assessments of progression, with 91 percent of the events occurring within 30 days of each other. This highlights the study's reliability and its robust design.

As Dr. Abramson discussed, complete response rate is an important clinical endpoint predicting long-term favorable outcomes and a key secondary endpoint of this study. With the longer follow-up,

CR rates improved compared to the primary analysis. Glofit-GemOx achieved a 58.5 percent CR rate, more than double that of the R-GemOx arm, which at 25 percent is consistent with historical and contemporary data. This 33.2 percent absolute difference in CR rates underscores Glofit-GemOx's ability to drive deep remissions. Together, the overall survival, PFS, and CR data highlight the potential of Glofit-GemOx to meaningfully improve outcomes in relapsed/refractory DLBCL.

Switching to safety, the results of the STARGLO study provide a comprehensive assessment of the safety profile of Glofit-GemOx, which is consistent with the known risks of the individual components. It is important to highlight that patients in the Glofit-GemOx arm were able to receive a higher median number of treatments of cycles compared to those of the R-GemOx arm, contributing to longer exposure and potentially higher event rates.

Grade 5 adverse events were predominantly infection related, a risk that is well recognized

in this patient population and with anti-lymphoma therapies. The most common grade 3-4 adverse events were cytopenias, also consistent with the known profiles of gemcitabine and oxaliplatin. Cytokine release syndrome, known as CRS, and immune effector cell-associated neurotoxicity syndrome, known as ICANS, are not unique to glofitamab.

These events are well recognized in the context of T cell engaging in cellular therapies for lymphoma with established grading criteria and management protocols. In the STARGLO study, CRS was most commonly observed during the first dose of glofitamab and was predominantly grade 1, typically presenting as fever, manageable with antipyretics and corticosteroids. ICANS were infrequent, predominantly low grade, and reversible.

Importantly, infection risk can be mitigated through a proactive approach that includes infection prophylaxis, careful monitoring, and avoidance of treatment during active infections, principles well understood and routinely applied by physicians managing similar therapies. Overall,

the safety risks are well characterized, aligned with the clinical expectations for this regimen, and are supported by clear and established management guidelines.

Now that we've seen the efficacy and manageable safety, we'll shift back to the efficacy and look at the subgroup outcomes compared to the overall population.

Subgroup analyses were conducted across 26 prespecified factors, encompassing 77 individual subgroups. Here I'm showing a selected set of relevant subgroups. While not powered for definitive subgroup comparisons, results were directionally consistent across most subgroups favoring glofitamab-GemOx. Apparent differences should be interpreted with caution due to wide confidence intervals.

When we look at the age of the patients in this study, we saw that the benefit was consistent regardless of age. Additionally, consistency was observed across the clinically meaningful stratification factors of refractory disease status

and number of prior lines of therapy. Importantly, even in primary refractory hard-to-treat patients, they also derived a benefit comparable to those who were not.

When examining subgroups based on race and geographic region, potential inconsistencies emerged. These findings were unexpected, and we wanted to conduct a detailed evaluation to help us understand them further. Because of the strong correlation between race and region in the data set, our further analysis focused specifically on regional outcomes. Here's a more detailed look at the efficacy outcomes for the three prespecified regions of North America, Europe, and Asia Pacific.

In Asia Pacific, the overall survival hazard ratio was 0.41 and the PFS and CR rates were consistent with the ITT. In Europe, while we saw an overall survival hazard ratio of 1.09, there was a directionally consistent benefit in favor of Glofit-GemOx in PFS and CR. However, in North America, which as we mentioned earlier was the smallest regional subgroup with 25 patients, we

observed notable differences compared to the ITT population. The overall survival and PFS hazard ratios were above 2, and we saw CR rates of 40 percent in both treatment arms. These results were unexpected and warranted further investigation.

First, what we wanted to do, we wanted to review Glofit monotherapy data, the efficacy, and the clinical pharmacology across various regions; then we analyzed baseline characteristics by region for potential imbalances. Together, these insights help us contextualize the findings and explore possible drivers of variation.

This slide illustrates why regional differences were not expected in the STARGLO study. While the full data are in your briefing materials, I want to highlight two key takeaways.

First, prior data from the glofitamab monotherapy program showed consistent CR rates among regions, reinforcing expected regional uniformity in activity. Second, pharmacokinetic analyses from both monotherapy, shown here, and

STARGLO show comparable drug exposure across regions with similar efficacy across the same concentration range. Together, these findings support that Glofit performed as expected across geographies, even in combination with GemOx. So overall, the pharmacokinetic and exposure-response data do not support a pharmacological explanation as to why glofitamab would perform differently across regions.

This brings us to our next question. Did baseline differences impact the outcomes?

Here, we examine baseline characteristics across North America, Europe, and Asia Pacific. The most notable observations were among the 25 patients enrolled from North America, where a clear imbalance in high-risk features between treatment arms were identified. Specifically, in the Glofit-GemOx arm, there was a higher proportion of patients who were primary refractory, 80 percent versus 40 percent. As highlighted by Dr. Abramson earlier, primary refractory disease represents the highest risk, hard-to-treat population associated

with particularly poor outcomes in relapsed/refractory DLBCL.

All deaths in North America occurred in patients with primary refractory disease, two in the R-GemOx arm and eight in the Glofit-GemOx arm. This imbalance in a high-risk subgroup is a confounding factor, as it is both prognostic and unequally distributed between the treatment arms. This helped explain the overall survival hazard ratio above 2 in North American patients and underscores the importance of interpreting this regional result within the context of baseline disease severity.

With that overview, I will now turn over to Dr. Sethuraman, who will present additional subgroup analysis to further explore potential regional inconsistencies.

Applicant Presentation - Venkat Sethuraman

DR. SETHURAMAN: Thank you, Dr. Boyer.

My name is Venkat Sethuraman. I lead Data Science and Analytics at Genentech. Today, I'll walk you through exploratory and sensitivity

analysis conducted to better understand the regional differences in the STARGLO trial. My presentation will cover three things: our evaluation of baseline characteristics, performance of treatment and control arms, and impact of new anti-lymphoma therapy, or NALT, on the trial outcomes.

Recognizing the small sample size of the North America subgroup, and to strengthen our analysis, we combined groups into two broader categories. This was based on the shared phenotypic and genotypic traits. You can see North America, Europe, and Australia have 143 patients and Asia has 131 patients. The baseline characteristics appear to be balanced for most of the factors between the treatment arms also across regions. This includes the highly prognostic primary refractory group that Dr. Boyer spoke to.

As noted by the agency, there are still some imbalances across regions for baseline factors. Rather than looking at each factor and the corresponding treatment outcome in a univariate

setting, we can estimate treatment effect through a multivariable analysis. This is exactly what we did. We performed a multivariable analysis, including the seven factors that FDA highlighted. Analysis shows consistent results with the ITT with a hazard ratio of 0.59. With this understanding of the baseline impact, let's look at each efficacy point in a bit more detail.

In North America, Europe, Australia, and Asia subgroups, overall, results are consistent with the ITT population. The key secondary endpoint of PFS shows directly consistent benefit in the Glofit-GemOx arm compared to the ITT population. Also, the CR rate shows substantial benefit for Glofit-GemOx, consistent with the ITT population.

Now, let's look at the primary endpoint, overall survival, in the North America, Europe, and Australia subgroup. In this particular group, we see that the hazard ratio is 1.06 for the overall survival, which we will investigate a little bit further. A key question that has been raised here

is the performance of the treatment and control arm by region, so let's examine the overall survival performance for Glofit-GemOx by region.

Here, we see the KM curve for the Glofit in the ITT population, demonstrating a meaningful survival. When we focus on the Asia subgroup, as well as compared with North America, Europe, and Australia, we observe consistency in the overall survival for both regions. The curves are remarkably aligned with the ITT population, reinforcing their robustness and the generalizability of Glofit-GemOx treatment across the regions. Our next step is then to understand how R-GemOx performed in the two regions compared to the historical data.

First, we look at the contemporaneous studies and real-world data for R-GemOx in a similar population. Here, it's reported that the median overall survival is between 8 to 13.5 months. When we compare this both to the ITT and the Asia subgroup of the STARGLO trial, we see that it is very much aligned with the expected

range of 8 to 13.5; however, patients treated with R-GemOx in North America, Europe, and Australia region showed better than expected outcome, as highlighted here, with 27.8 months median overall survival. So if there is any question, it is the R-GemOx overperformance in the North America, Europe, and Australia region.

So to understand why R-GemOx performed better than expected, we analyzed the use of new anti-lymphoma therapy, or NALT, across the regions. First, we found that the patients in the R-GemOx arm, regardless of the region, received more NALT due to the higher percentage of patients experiencing treatment failure. Second, in the North America, Europe, and Australia subgroup, we see the highest use of highly effective NALT, such as CAR T bispecific antibodies, while in Asia grouping, we see such usage being very limited.

Now that we see that there is an imbalance in NALT utilization between the arms and the type of NALT between the regions, we want to understand how this impacts the trial outcomes, so let me

orient you to this plot.

You might be familiar with this type of data presentation referred to as swimlane plot, where each line represents the overall survival for an individual patient, contributed both by study treatment and by subsequent therapy. As you can see, the survival appears similar between the two treatment arms. Recall the hazard ratio for this particular population was 1.06.

Now, in red, if we overlay the survival observed after patients failed treatment, and if they initiated subsequent therapy, you can see that a significant portion of the overall survival in R-GemOx arm is driven by NALT, accounting for nearly 40 percent compared to 11 percent in the Glofit arm.

So, to understand the true treatment effect, when NALT is not available, we use an inverse probability sensor weighting approach, which is IPCW, and adjusted analysis, which is a well-accepted statistical approach, for estimating OS in this particular context. Once we perform

this particular adjustment, we see that OS hazard ratio for the North America, Europe, and Australia subgroup is 0.73. This is similar for the ITT.

As you can see, NALT had a large impact on the OS outcome observed in the R-GemOx arm. As you heard from Dr. Abramson, patients not achieving complete response may start NALT prior to disease progression; therefore this impacts PFS estimation similar to what I showed you with the OS estimation. A quarter of the patients in the R-GemOx arm had NALT compared to 4 percent in Glofit. IPCW adjusted hazard ratio for PFS is 0.51, which is also consistent with the ITT population, which is not shown here.

As a next step, we looked at the endpoints that either considered NALT as an event or not affected by NALT, EFS, which we all know is a clinically meaningful and regulatory accepted endpoint in this particular disease setting. Here, NALT, along with disease progression and death, is considered as an event. The EFS analysis in this subgroup shows a clear prolonged separation in the

two treatment arms. The hazard ratio is 0.58, and it is consistent with the ITT population. When we look at the CR rates, a clinically important endpoint which is not impacted by NALT, we see a consistent benefit favoring Glofit-GemOx in North America, Europe, and Australia, a 22.5 percent improvement in line with the ITT population.

So, to summarize, when we look at the endpoints that account for NALT, we see a consistent benefit favoring Glofit-GemOx over R-GemOx also in the North America, Europe, and Australia subgroup, which is in line with what we observed in the ITT population.

In summary, we know that subgroup point estimate is not a sound assessment of the true benefit in the U.S. A multivariable analysis adjusting for prognostic factors shows consistency in the OS outcome. The outlying performance of R-GemOx in North America, Europe, and Australia is primarily driven by NALT, and the Glofit-GemOx performs consistently across all the regions.

In conclusion, in this context, the best

unbiased estimate for a treatment effect by any subgroup, including the country the United States, should be the ITT estimate. In the global population, the results are statistically robust, statistically significant, in all of the clinically relevant endpoints.

With this, I'd like to hand over to Dr. Patel to discuss the relevance of the STARGLO trial to DLBCL patients in the U.S. Thank you.

DR. VASAN: Sorry to interject. So, it's 9:15 right now, which is actually at time, and we do have a tight schedule. In the interest of being fair to the FDA, I'll allow for five more minutes total from Genentech for the next two presentations. Thank you.

Applicant Presentation - Krish Patel

DR. PATEL: Thank you.

My name is Krish Patel. I'm a medical oncologist and the Director of Lymphoma Research at the Sarah Cannon Research Institute. These are my disclosures, which include being a paid consultant for the sponsor.

The goal of treatment of relapsed/refractory DLBCL is cure. The hallmarks of curative therapies in this setting are those that maximize depth of response measured by complete response, minimize need for subsequent therapy, and maximize survival without presence of the disease.

There are several patient characteristics that I find important when recommending therapy to patients. Patients with primary refractory disease have the worst prognostic outcomes. These patients often have kinetically aggressive disease that progresses over days and weeks, and these patients typically need therapies immediately available that can produce rapid responses.

Most patients with DLBCL are older adults, many with comorbid illnesses, in this setting, they will often make choices about therapy that reflect practical considerations. Many patients may not have reliable transport, may be reliant on caregivers, or unable to displace themselves from home to seek travel in other centers.

Biologic factors such as cell of origin,

which the FDA mentioned, are not relevant in the relapsed/refractory setting, where they do not hold the same prognostic value that they do in the frontline setting and are typically not used for therapy selection.

How do we apply these factors to the STARGLO study? First, we see that Glofit-GemOx was highly efficacious and associated with an overall survival benefit, even in high-risk patients such as those with primary refractory disease. We also see that the therapy was associated with a high complete response rate and a good event-free survival, a clinically meaningful endpoint in the treatment of relapsed/refractory DLBCL. Furthermore, the safety profile of Glofit-GemOx was consistent with glofitamab monotherapy, a treatment that is widely available and used safely in the community setting.

This is a fundamental aspect of the study. This is a key challenge in the clinic. Many patients, as you heard from Dr. Abramson, are not able to access therapies like CAR T cell and stem cell transplant, even when medically eligible.

Patients need more therapies in this setting, and they will often choose therapies that can be given safely and close to home.

The most common setting for treatment of relapsed/refractory DLBCL is in the community, and rituximab-based chemotherapy is given to approximately 50 percent of patients in the U.S. When we look at patients in the U.S. receiving R-GemOx in real-world evidence studies, we find that these patients are similar to those in the overall STARGLO study, with a similar median age, IPI score, number of prior lines of therapy, and similar proportion of patients who are primary refractory.

So what does a discussion around second-line treatment and transplant-ineligible patients look like in the clinic?

When we're in the clinic, these are conversations that often start with referring oncologists reaching out for guidance on their patients. Often I may start this discussion talking about the expected outcomes for CAR T-cell

therapy in this patient population. Unfortunately, many times my colleagues will tell me, "Dr. Patel, this patient that I'm talking to you about is too sick to travel. They don't have the time to wait for this therapy. They need something more immediately available." Many patients are not even referred to have these discussions because the feasibilities of CAR T-cell therapy are well known and expected to put it out of reach.

Ultimately, only around 15 percent of patients in the U.S. receive CAR T-cell therapies in this setting. Unfortunately, that means the conversation for most patients in the U.S. reverts to this. "What is available in their community setting? Rituximab-based chemotherapy." And we have already heard about the poor outcomes associated with this option. Patients in the U.S. need more options for therapy.

Tomorrow, when inevitably this conversation happens again, I would like to tell my referring physician colleagues, and their patients, that there is another treatment option, glofitamab and

GemOx, a treatment that in a randomized clinical trial demonstrate an improvement in overall survival in all key primary efficacy outcomes compared to rituximab chemotherapy, a treatment that, frankly, with the caveats of cross-study comparison, has efficacy in the range for the approved CAR T-cell option in this setting. Importantly, as I will show you, Glofit-GemOx can be given in a variety of treatment settings, including the community, and can be given when, where, and how patients need it.

There has been a lot of work in the last decade to improve access to CAR T-cell therapies, and today in the United States, we have 190 centers that are capable of delivering this therapy to patients. Unfortunately, that is not enough to meet the needs of U.S. patients. In contrast, bispecific antibodies for lymphoma since their initial approval have been successfully and safely delivered in over 700 U.S. sites, improving access to much needed therapies for patients in the U.S.

Overall, the STARGLO study is representative

of patients in the U.S. The types of patients that we see in the U.S., including high-risk patients, are present in the STARGLO population. Glofit-GemOx delivers a high rate of complete response, reduces need for subsequent treatment, improves overall survival, and offers a potential for cure. We need this therapy for U.S. patients.

Thank you. With that, I'll turn it back to Dr. Fuchs.

DR. VASAN: Sorry. Out of the interest in time, I think we're going to have to move on to the FDA presentation.

DR. FUCHS: Can I just do my last slide?

DR. VASAN: Yes, I'll allow that.

Applicant Presentation - Charles Fuchs

DR. FUCHS: Thank you, Dr. Vasan.

I'm sorry. I'm standing in front of the mic. As I said, I will just turn to my final slide in the interest of time. Thank you for that permission.

Forums such as today's ODAC are a critical part of our responsibility to patients. Following

concurrent reviews of the STARGLO data, Glofit-GemOx is now approved in over 30 countries, including the European Union, and was selected as a Category 1 treatment recommendation by U.S. lymphoma experts for the NCCN.

STARGLO was a rigorously conducted randomized, global, phase 3 trial that delivered the highest level of clinical evidence, a statistically significant practice-changing improvement in the indisputable endpoint of overall survival. Based on the consistent efficacy of Glofit-GemOx across regions of the world, including North America, and the other reasons articulated by my colleagues, the benefit of Glofit-GemOx documented in STARGLO is applicable to U.S. patients and supports regular FDA approval for patients in the U.S.

We thank you for the opportunity to present these data. This now concludes our presentation.

Dr. Vasan, we'll now return it back to you.

DR. SEO: Hi. This is Jessica speaking. I apologize for the interruption, Dr. Vasan. I have

been informed that the FDA Commissioner and new Director of CBER, Dr. Prasad and Commissioner Makary, are here.

Welcome. And if you have some remarks, Dr. Vasan, is it ok if they have the floor?

DR. VASAN: Yes.

DR. SEO: Okay. Thank you.

FDA Welcome

Martin Makary and Vinayak Prasad

DR. MAKARY: Well, thank you. I'll just sit right here, if that's ok.

Welcome, everybody. We just wanted to say hello. As a surgical oncologist, my heart is here, and I want to be listening to STARGLO and every other thing that glows from this meeting. It's good to see Dr. Pazdur, Jacqueline, and the group here.

As you know, Dr. Vinay Prasad is the new Director of CBER and a hematologist/oncologist. We're on our way over to a roundtable on talc, which has been identified as a carcinogen by international bodies and some pretty comprehensive

reviews of more than 30 studies. And it's almost as if we're ignoring the data because of what it means for our food supply. Talc is in the common candies and gum. It's in rice. It's in many things that we consume on a day-to-day basis.

It's in medications, actually. It's in the number one most common medication in the United States, the number 1, 3, 9 and 10 most common medications in the United States. Twenty-plus million people are consuming talc after we've recognized, as a society, that it may be a carcinogen from its topical use.

So we're on our way over there now. So, for that reason, we're not going to be able to stay and learn about this interesting data. But I wanted to just say thank you for contributing your time to this very important endeavor. Dr. Pazdur and I have talked about the importance of your contributions and a few of these emerging issues that we have to consider as an agency. What do we do with trials where all of the enrollees are in China? Are these trials that we can make big

decisions in our national interest?

So, those are questions that are in front of you, among many other questions, so we look forward to hearing your input.

Dr. Prasad, do you want to just say hello?

DR. PRASAD: Thank you, Dr. Makary.

It's a pleasure to see you all again. Vinay Prasad at CBER, and looking forward to listening to your meeting today and future meetings. It's been about 10 years since I was last in DC at the National Cancer Institute; a lot of familiar faces. And once again, my admiration for your important work here today, and looking forward to meeting you all in the weeks to come. But now, it's back to reading a few more memos to get up to speed. You've got to read a few memos. Thank you.

DR. VASAN: Thank you, Commissioner Makary and Director Prasad. And thank you, Genentech.

We will now proceed with FDA's presentation, starting with Dr. Nicole Sunseri.

FDA Presentation - Nicole Sunseri

DR. SUNSERI: Good morning. I am Dr. Nicole

Sunseri. I'm a hematologist/oncologist and a clinical reviewer in the lymphoma team at the Division of Hematologic Malignancies II at the FDA. I will present the FDA's perspective and concerns regarding the STARGLO trial results as they apply to a U.S. patient population with relapsed/ refractory diffuse large B-cell lymphoma.

The members of the FDA review team are listed here. My presentation reflects their collective input. The FDA's discussion for today's ODAC meeting will focus on several notable observations from the STARGLO trial, specifically the following:

Although STARGLO was a multiregional trial, it has substantial representation of a single region and limited enrollment of the U.S. The trial demonstrated inconsistent efficacy results across subgroups, specifically based on region, and the enrolled population has notable differences based on region.

The FDA's discussion for today's ODAC meeting, I will be discussing those discussion

points in greater detail, but it's important to first take a step back to see the forest through the trees.

The FDA's analysis of the STARGLO trial has culminated in two major concerns. The regional differences and inconsistent treatment effect raise uncertainty about the robustness of the overall STARGLO trial results and the treatment effect. These regional differences and concerns with the results call into question the applicability of the findings to a U.S. patient population and the U.S. medical practice.

The FDA's discussion will be divided into two main sections. First, I will present an overview of the STARGLO efficacy results, providing evidence that the trial, though multiregional, has a large representation of a single region with few U.S. patients and that the efficacy results are inconsistent between large subgroups. The second portion will then go over an evaluation of the regional differences in the trial population, focusing on key characteristics of the patients,

their disease, and trial processes that may have impacted the trial and raise further uncertainty in the applicability of its results to a U.S. patient population.

To begin, I will discuss the STARGLO efficacy results.

You have already heard the top-line results from my FDA colleagues and the applicant, but briefly, the STARGLO trial was a 2 to 1 randomized trial comparing glofitamab combined with gemcitabine and oxaliplatin, or Glofit-GemOx, to rituximab combined with gemcitabine and oxaliplatin, or R-GemOx, in patients with relapsed or refractory diffuse large B cell, following at least one prior therapy and considered transplant ineligible.

In the intent-to-treat, or ITT, population, treatment with Glofit-GemOx demonstrated a statistically significant improvement in its primary endpoint of overall survival, as well as in two of the three key secondary efficacy measures, progression-free survival and complete response

rate. However, this improvement in OS was not consistently observed in all subgroups, particularly in those based on race and region, as shown here in this forest plot.

Specifically, as denoted by the blue asterisk, for these subgroups, the point estimate for the hazard ratio of OS is above 1, suggesting that the favorable trend is not present for patients enrolled in Europe and North America or in patients identifying as White race. This marked difference in treatment effect between subgroups, especially as it is observed in large subgroups, raises uncertainty that the treatment effect may apply to the total population.

Although the treatment effect differences were observed for both regional and racial subgroups, our subsequent analyses will focus on subgroups based on region. This table illustrates the distribution of the STARGLO ITT population by region and by the initial prespecified regional subgroups of North America, Europe, and rest of world. While STARGLO is a multiregional trial

enrolling from several countries and regions, the FDA noted an overall low enrollment from North America, which is exclusively from the United States at 9 percent, but a larger representation of patients enrolled from Asian countries, China, Korea and Taiwan, which accounted for almost half, 48 percent, of the total ITT population.

One of the reasons for this large representation of patients from the Asian countries is that the STARGLO protocol specified, as shown, that at least 80 patients from China, Hong Kong, and Taiwan, sites the applicant noted were recognized by China's National Medical Products Administration, were planned to be enrolled to support a marketing application in China. As a result, 34 percent of the ITT population was enrolled from China and Taiwan, and out of the 48 percent of the ITT population that was enrolled from the Asian region, 72 percent were enrolled solely from China and Taiwan. However, there were no minimum enrollment requirements for other countries or regions, which may have ensured a more

balanced representation in the trial.

For further subgroup analyses, the FDA divided the ITT population into two regional subgroups, an Asian regional subgroup, which consisted of the 48 percent of patients enrolling from the China, Korea, Taiwan countries, and a non-Asian regional subgroup, which consists of the remaining 52 percent of the patients that enrolled from the U.S., Europe, and Australia. The update considered this revised grouping to be appropriate for analysis based on similar intrinsic and extrinsic factors, medical practice, and available therapies, as well as long-standing participation in global clinical research.

This figure shows the FDA analysis of overall survival based on region. The solid lines represent the Asian region and the dotted lines represent the non-Asian region, with red denoting patients in these regions treated with R-GemOx, and blue is for those treated with Glofit-GemOx. As shown in the tables, the Asian region has an OS hazard ratio of 0.39, while the non-Asian region

has an OS hazard ratio of 1.06. These are striking regional differences which will be explored during this presentation.

A similar pattern is observed for patients in these regional subgroups for progression-free survival, as shown in this figure. In the Asian region, there was an approximately 18-month improvement in median progression-free survival; however, in the non-Asian region, there was a marginal improvement, a median PFS of approximately 1.4 months.

This differential treatment effect was also present in the regional comparison of response rate. As depicted in the bar graph, sizable increases in overall response rate and complete response rate were observed in patients in the Asian region treated with the Glofit-GemOx, shown in blue, compared with the R-GemOx, shown in red. This is in contrast to the non-Asian region with much smaller differences in response rate.

While the concerns regarding the STARGLO efficacy results are informed by subgroup analyses,

as Dr. Gormley discussed earlier this morning, subgroups provide valuable information about the consistency of the benefit-risk profile across important patient populations. Thus, assessments demonstrating consistent effects in subgroups offer greater assurance that the treatment effect observed truly applies to the entire population.

In terms of the STARGLO regional subgroups, it is important to note that the subgroups in question are not small relative to the overall size of the trial, with each group representing almost half of the ITT population. Additionally, the differential treatment effect observed was demonstrated across all of the major efficacy measures, including OS, PFS, CR rate, and ORR.

To assess the regional differences amongst the efficacy endpoints, the FDA conducted an exploratory post hoc analysis using an interaction test. While there are limitations to this type of analysis, an interaction test is a statistical analysis intended to test for the presence of differential treatment effects among two or more

subgroups, where a significant test -- for instance, one where a p-value is less than 0.05 -- indicates that the treatment effect observed is different among subgroups compared. The interaction test performed by the FDA resulted in nominal p-values which were significant for OS, PFS, and ORR, suggesting that the treatment effects on these endpoints were different between the Asian and non-Asian regional subgroups and less likely due to chance.

To summarize the first portion of the discussion, the ITT population in the STARGLO trial demonstrated statistical improvement in its primary endpoint of OS and two of three key secondary endpoints; however, we have concerns whether these results are robust or applicable to the U.S. patient population.

First, the STARGLO trial, while technically a multiregional trial, had a large representation of a single region with almost half of its ITT population comprised of patients enrolled in Asian countries and only 9 percent of its patients from

the U.S. The treatment effect across all major efficacy endpoints was inconsistent between the Asian and non-Asian regional subgroups. And lastly, given the size of the Asian subgroup and the magnitude of the treatment effect, it is likely that the overall study results are being driven by the Asian regional subgroup.

When reviewing an application for approval, the FDA is tasked with determining whether there is a favorable benefit-risk of the treatment based on the data provided. When relying on results from a multiregional clinical trial for an application, the FDA Multiregional Clinical Trial Draft Guidance states "that it is paramount consideration for the FDA, when evaluating such oncology trials, whether the results are applicable to the intended use population in the U.S. and to the U.S. standard oncological care."

The guidance provides a framework for assessing the applicability of trial results to the U.S. population. Specifically, the guidance elaborates on the assessment of various intrinsic

and extrinsic factors that may be present in these populations, such as patient-related factors like age, disease-related factors, and healthcare system-related factors like pre- and post-therapy availabilities. These can impact a patient's response to therapy and the applicability of the subsequent results to an intended patient population in the U.S.

With this guidance in mind, we will proceed to the second portion of the presentation, a discussion of the major regional differences observed in the STARGLO trial and why there is uncertainty regarding the applicability of the overall trial results to a U.S. patient population. As we navigate this portion, we will be evaluating the two regional subgroups based on patient-related factors like age and race, disease-related factors like cell of origin and prior therapies, and healthcare system factors like availability of subsequent therapies. For the first part, we will focus on patient- and disease-related factors and highlight the differences between the regional

subgroups.

Regarding general demographics, our key observations included, the patients enrolled in the Asian region appear to be substantially younger than their non-Asian counterparts, with a median age of 62 years compared to 71 years. This is particularly evident when examining age subgroups, where 55 percent of the patients in the Asian region were under 65 years of age compared to only 21 percent in the non-Asian region. Both subgroups were largely homogeneous in terms of race, with the Asian region being 100 percent Asian and the non-Asian being 80 percent White. Few other races were represented.

These demographic features of the STARGLO population, particularly in the Asian region, contrast with the U.S. epidemiological data. Based on SEER data from 2017 to 2021, the U.S. diffuse large B-cell population is estimated to have an overall older age group, with a median of 69 years with 60 percent over 65 years old, and a more heterogeneous racial and ethnic composition.

Another key area particularly relevant to the STARGLO trial is the reason for transplant ineligibility. This table shows the various reasons that were considered for transplant ineligibility in the trial. It is important to note that in the U.S. and Europe, patients generally are considered transplant ineligible based on fitness criteria such as advanced age, multiple comorbidities, poor performance status, or insufficient response to salvage therapy.

While these typical reasons for transplant ineligibility appear to be more prevalent in the non-Asian region, they were not predominant in the Asian region. In fact, the majority of patients, 65 percent, in the Asian region had patient refusal as the reason for transplant ineligibility. Patient refusal as a criterion does not allow for a comprehensive assessment of the patient's fitness for transplant. It is unclear whether these patients refused due to transplant unavailability or other reasons. Given that transplantation is used less frequently in Asian countries compared to

the Europe or U.S. regions, it is possible that many of these patients who refused transplant might represent a different population than those that are transplant ineligible in the U.S.

Regarding disease-specific factors, the agency examined characteristics known to have prognostic significance, such as primary refractory disease, bulky disease, more advanced stage disease, among others. For the most part, these baseline characteristics were similar between the two regions, with only subtle differences noted; however, one difference noted was the higher percentage of patients in the Asian region with early relapsed disease, defined as a relapse within 12 months of the first line of therapy. These patients may represent a more refractory or aggressive subset, who may not be ideal candidates for the R-GemOx control arm as a salvage treatment choice.

Another notable disease characteristic is cell of origin. Diffuse large B-cell lymphoma is a heterogeneous disease that can be characterized

into subgroups based on cell of origin, which refers to the type of B cell from which the lymphoma develops. Classification can be done by either immunohistochemistry or by the preferred method of gene expression profiling. The latter method divides diffuse large B cell under three main groups: activated B-cell like or ABC; germinal center B-cell like or GCB; or the smaller group, the unclassified diffuse large B cell.

The classification by cell of origin, distinguishing particularly between GCB or ABC type, has prognostic significance. In the frontline setting, several studies have shown inferior outcomes in the patients with ABC type to chemoimmunotherapy compared to those with GCB type. Prognostication based on cell of origin in the relapsed/refractory setting is less clear but does appear to still have some significance, as several studies have shown differential responses to therapy based on cell of origin, as shown in this slide.

The characterization of cell of origin is of

particular importance in our evaluation of STARGLO since studies have suggested that there is a regional prevalence of the ABC type. There is a higher percentage of ABC type diffuse large B cell in Asian countries, where the ABC type was found to be approximately 60 percent compared to other parts of the world, where it ranged from 32 to 40 percent. Thus, it is possible that a regional imbalance in the cell of origin subtype could have an impact in the overall study result because of differential responses to therapy.

In STARGLO, cell of origin classification via gene expression profiling was performed centrally as an exploratory endpoint. At study entry, 59 percent of all the patients had samples available for testing; 49 percent were tested in the Asian region and 68 percent in the non-Asian region. Of those tested, there was a notable predominance of the ABC type diffuse large B cell in the Asian region, 70 percent, compared to 42 percent in the non-Asian region. Importantly, this high percentage in the Asian region aligns

with the prominence of this cell of origin type in Asian countries reported in the literature.

Lastly, the FDA examined the prior therapies that the patients received. Overall, the subgroups had similar lines of therapy, and most patients had been exposed to an anthracycline and prior CD20-based therapy; however, a few notable differences were present. A small but higher number of patients were exposed to prior CAR T therapy in the non-Asian region. Conversely, a higher percentage of patients in the Asian region were exposed to lenalidomide-containing regimens and other regimens, which were not generally standard of care options in the U.S., further separating this patient population from that in the U.S.

To summarize the agency review of patient- and disease-related factors, the FDA found several regional differences, most notably in the Asian region. Taken together, these differences paint the picture of a different type of baseline patient in the Asian region than who would be expected in

the U.S. In particular, the younger age, the majority refusing transplants; the different disease characteristics with more early relapsed disease, a higher percentage with the ABC type; and the prior therapy differences suggest that these patients represent a different patient population than those in the U.S., which could lead to a differential response to therapy.

Besides looking at the baseline patient and disease characteristics, the agency also examined healthcare system factors and trial processes that may have differed by region and had a potential influence on the results, impacting events prior to or during the clinical trial.

The applicant has attributed some of the observed regional differences due to NALT. NALT, or new anti-lymphoma therapy, is used to describe the subsequent therapy a patient with lymphoma may receive after discontinuation of study treatment. NALT is an important item to consider in the STARGLO trial, as it can impact a patient's overall survival.

Overall survival as an endpoint incorporates NALT. The analysis of OS is assessed as the time of randomization to death, regardless of NALT. In a multiregional trial with similar regional practices and available therapies, the presence of NALT and types of NALT would be similar across regions such that the impact of NALT on OS assessments would be uniformly distributed.

As depicted in the figure, NALT would occur after discontinuation of therapy, generally after progression, and may impact the efficacy outcome of OS. Importantly, receipt of NALT generally should have minimal, if any, impact on PFS and does not impact response rate.

In STARGLO, a higher percentage of patients received NALT following treatment with R-GemOx compared to the Glofit-GemOx arm, 58 versus 27 percent, respectively. But the overall percentage of patients receiving any NALT by region within each treatment arm was similar; so region did not appear to impact whether the patient received NALT.

However, the types of NALT received did differ by region, with higher percentage of patients in the non-Asian region receiving novel NALT regimens. These types of agents, which would be part of the standard options in the United States, include antibody drug conjugates like polatuzumab; the CD19-directed antibody, tafasitamab combined with lenalidomide; CAR T; bispecific T-cell engagers; and stem cell transplant.

This imbalance was noted in both treatment arms. In the R-GemOx arm, 40 percent of patients in the non-Asian region were treated with these agents compared to 24 percent in the Asian region. In the Glofit-GemOx arm, 19 percent of these patients in the non-Asian region were treated with these agents compared to 6 percent in the Asian region.

Although there were differences in the types of NALT received, the associated sample sizes are small, such that it is not possible to precisely characterize the impact of NALT on OS. However,

the observed differences in NALT do reflect there are differences in the available therapies in these regions and again calls into question the applicability of the result to the U.S. patient population.

As previously shown, NALT should not greatly impact the other efficacy endpoints like PFS and does not impact response rate. As both the PFS and response rates demonstrate a similar inconsistent treatment effect by region, the differences in the type of NALT received do not explain the results.

When assessing trial processes that may impact outcomes, the agency examined the potential for early or unscheduled response assessments. An early assessment, which could be due to bias given the open-label nature of the trial, or due to actual symptomatic deterioration or progression, would affect PFS and potentially lead to a differential efficacy outcome.

The FDA assessed the timing of disease assessments in the STARGLO trial. As shown in the table on the left, both regions had a similar

proportion of patients with earlier tumor assessments in the Glofit-GemOx arm at 17 percent and 20 percent, mostly occurring within 1 or 2 weeks of the planned cycle 4 assessment. In contrast, in the R-GemOx arm, the Asian region had a much higher proportion of patients with earlier tumor assessments compared to the non-Asian region, 56 percent versus 22 percent, respectively, and these assessments were several weeks prior to planned cycle 4 assessment, as shown in the bar graph on the right.

The actual reasons for these early assessments in the Asian region in the R-GemOx arm are not clear and may suggest either bias, given the open-label nature of the trial and these patients being on the control arm, or earlier concerns for progression in this region.

So, to summarize the examination of healthcare system factors also paints a picture of a different type of patient in the Asian region than the U.S., in this case, most likely due to medical practice differences. Specifically,

patients in the Asian region did not have the same categories of NALT as are available to the U.S. patients. Additionally, there was a higher proportion of earlier assessments in the Asian region on the R-GemOx control arm that may reflect a bias or could have reflected a different more aggressive underlying disease. Again, it is important to reiterate that NALT generally should not impact PFS and does not impact response rates.

Lastly, I will discuss two other areas where differences were noted, treatment duration and treatment discontinuation.

Before reviewing the data on treatment duration, I'd like to review the protocol-specified treatment for this trial. Both regimens have the same GemOx duration of 8 cycles administered every 21 days. Of note, the Glofit-GemOx and R-GemOx regimens are not balanced.

Glofit-GemOx has four additional cycles of active treatment with glofitamab monotherapy and also includes pretreatment with obinutuzumab, a second generation anti-CD20 monoclonal antibody

that may offer additional pretreatment tumor debulking, which is not built into the R-GemOx arm. Additionally, the R-GemOx schedule is once every 3 weeks; however, at many institutions in the U.S. and elsewhere, this regimen would be administered more frequently at once every 2 weeks given the aggressive nature of the lymphoma.

The actual GemOx treatment duration in the ITT population, which per protocol should be about 5.5 months or 8 cycles for each arm, was different between the arms. Patients in the Glofit-GemOx arm received GemOx at a median of about 4.8 months, so approximately 8 cycles, while those in the R-GemOx arm had GemOx administered at a median of 2.1 months, approximately 4 cycles.

As shown in this figure, this difference in GemOx treatment duration in the R-GemOx arm was magnified when looking at the duration by region. The treatment duration of R-GemOx was shorter in the patients in the Asian region who received a median of 1.1 months compared to the median 3.1 months in those on the R-GemOx arm in the

non-Asian region. This shorter treatment duration is also reflected in the higher percentage of patients who discontinued R-GemOx treatment in the Asian region at 78 percent compared to 62 percent in the non-Asian region.

The discontinuation rate was not entirely unexpected given the treatment duration observations, but it was notable that there was also a regional difference in the reason for the discontinuation. While disease progression was the most frequent reason overall for discontinuation of R-GemOx, this rate was higher in patients treated in the Asian region.

Seventy-two percent of patients in the Asian region discontinued R-GemOx due to progressive disease compared to only 46 percent of the patients in the non-Asian region. The reasons for these differences in progression are not clear but could be due to some of the patient- and disease-related factors previously discussed.

Not all areas assessed demonstrated regional differences, and it is important to briefly review

the other areas examined by the agency review team. The agency did not note any regional differences in exposure due to body weight; in the quality of the locally sourced gemcitabine and oxaliplatin; in the outcomes based on the delayed enrollment and regional follow-up; or any major differences that could impact the study results in terms of the safety profiles of Glofit-GemOx or R-GemOx.

Collectively, these other factors when demonstrating differences again pointed to regional variations that may be attributable to different practices, including potential bias or differences in the underlying disease, which may differ from what would be expected in the United States.

In summary, the analyses discussed in this presentation reveal multiple regional differences observed in the STARGLO trial results. First, inconsistent treatment effects between regional subgroups were observed across all major efficacy measures, including overall survival, progression-free survival, and overall response rate, with interaction tests that further support

the existence of a differential treatment effect.

Several baseline patient and disease characteristics differed and could impact treatment response. For patients in the Asian region, there was a significant difference compared to the intended population in the United States, including age, transplant refusal, cell of origin, and prior therapy, which may not be representative of a U.S. patient population.

Lastly, aspects of healthcare system and trial processes notably differed by region, reflecting variations in medical practices compared to those encountered by U.S. patients. These included differences in the availability of subsequent anti-lymphoma therapies, or NALT, as well as earlier assessments and shorter treatment duration, potentially indicating bias or even earlier progression due to a more aggressive disease.

The issues identified by the FDA call into question whether the results of the STARGLO trial are robust and applicable to the intended U.S.

patient population. If we consider the OS results in the non-Asian region as true, there is a potential detriment in survival, with the results in the U.S. subgroup raising additional uncertainty.

Given the observed patient, disease, and healthcare factor differences, and observed inconsistencies in the treatment effects between Asian and non-Asian regions, there is significant residual uncertainty about the applicability of the overall results to a U.S. patient population and U.S. medical practice. It is incumbent upon the applicant to provide substantial evidence of safety and effectiveness for their product as it relates to a U.S. patient population and U.S. medical practice.

The FDA would like the committee to discuss how the differential results observed in the Asian and non-Asian regions impact the overall interpretation of the STARGLO trial results and the generalizability to a U.S. patient population. After that discussion, we would like the committee

to vote on the following question: Are the STARGLO population and trial results applicable to the proposed U.S. patient population?

I thank you for your attention, and that concludes my presentation.

Clarifying Questions

DR. VASAN: We will now take clarifying questions from the presenters. We have 25 minutes, and if there's additional time after the OPH session, we'll return to clarifying questions if there are more.

When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for my questions," so that we can move on to the next panel member.

Are there any clarifying questions for the

presenters?

First, Dr. Lieu?

DR. LIEU: Yes. This is Chris Lieu. I have a question for Genentech. There's clearly a pretty big discrepancy in terms of the NALT usage in the control arm compared to the treatment arm, and I just want to hear the sponsor's hypothesis in terms of why there's such a discrepancy to account for that.

DR. FUCHS: Dr. Lieu, I think what you're referring to is the difference, really, in highly effective NALT, namely the greater use of CAR T and bispecifics in non-Asian cohort as opposed to the Asian. Is your question as it relates to why the practice is different or how it might impact results, or both?

DR. LIEU: Well, there's certainly a discrepancy in the type of NALT used in the region, but there's also a difference in NALT between the control and the treatment arm.

DR. FUCHS: Yes.

DR. LIEU: So, actually, just a hypothesis

about both. I mean, certainly, the regional differences, I think it's understandable that they're going to be certain variations in practices by region, but I think my question is really more directed towards control versus treatment.

DR. FUCHS: Of course. I'm going to invite Dr. Abramson to come up to talk about our interpretation of that practice.

DR. ABRAMSON: Thanks, Dr. Lieu. Jeremy Abramson, Mass General. There is certainly a higher proportion of patients in the control arm receiving NALT compared to the Glofit-GemOx arm, and my interpretation of that is that the R-GemOx didn't work as well as Glofit-GemOx.

NALT is used when there is a treatment failure associated with that treatment. Fewer patients on R-GemOx achieved a complete remission, and that means more patients had a treatment failure, and would, therefore, require a new anti-lymphoma therapy with the goal of regaining disease control and improving that patient's outcome.

DR. FUCHS: And, Dr. Lieu, I just want to add one important caveat in terms of what was stated about the effect of NALT on progression-free survival, namely NALT can and does affect progression-free survival.

The slide that was presented by FDA had an arrow of NALT after progression. You heard from Dr. Abramson that actually in lymphoma, in contrast to solid tumors where I practice, it's very common to switch therapies if you don't get a complete response. Patients in STARGLO moved on to NALT before progression. If you do that, you censor progression. You influence progression-free survival.

So with all due respect, NALT did influence progression-free survival in this study, and does routinely in lymphoma.

DR. VASAN: Would the FDA like to respond?

DR. RICHARDSON: Yes. Thank you, Dr. Vasan.

Nicholas Richardson, FDA. I think that's an important point that you raised, Dr. Fuchs. So yes, in clinical practice, patients that don't

achieve a CR, there are considerations to initiate subsequent therapy. An important point from a regulatory perspective is when we assess the trial, we are really trying to determine whether the evidence supports that there is substantial evidence of effectiveness and safety.

So, when we think about how subsequent therapy may impact progression-free survival, if you initiate subsequent therapy in a patient that has not met criteria for progression and they are censored, it does not isolate the treatment effect of the product under investigation.

So, for those patients that did not achieve CR, and they achieved something less, and they initiated subsequent therapy in the absence of a defined progression event, and they are censored, it does not allow us to isolate the treatment effect. And that's an important regulatory consideration when we're thinking about the regulatory framework and the evidence required to support a favorable benefit-risk for patients here in the U.S.

DR. FUCHS: Let me just say that I totally understand. Obviously, the primary endpoint was overall survival, and STARGLO provided a 41 percent improvement in overall survival. My only point is that progression-free survival was influenced by NALT. And I just want to put that on the record simply because to state that it didn't would not be a fair characterization of what happened in STARGLO.

DR. LIEU: That concludes my question. Thank you.

DR. VASAN: Dr. Nooka?

DR. NOOKA: Thank you.

DR. VASAN: Please state your name.

DR. NOOKA: Ajay Nooka from Emory. My question is to the sponsor, based on two aspects. One is the control arm; the second one is safety.

So from a control arm perspective, dose-dense of R-GemOx is very common, as pointed out by the FDA. Why was there a choice of the every 3-week regimen for R-GemOx? And at the same time, could you provide me data of the rates of

discontinuation of the GemOx by the region, the backbone of GemOx by the region, that could have an impact on the endpoints?

My second question is about the safety. What supportive care was given for these patients across the regions? Is there any difference in the IVIG, any difference in the Neupogen usage, any difference in the antibiotic usage? So, if you can help me to clarify that, please.

DR. FUCHS: Thank you for that question. I was capturing the three parts. Remind me the first part of your question. Forgive me.

DR. NOOKA: The first part is a discontinuation of the GemOx backbone by the region.

DR. FUCHS: I think that was your second part. There was an earlier part to your question; 2 weeks or 3 weeks. Thank you. And I want to address all three parts of your question, Dr. Nooka.

With regard to 2 weeks versus 3 weeks, for those of us in the solid tumor world, I will just

tell you GemOx is a very common regimen, and it is very quite routine to use it either 2 or 3 weeks, every 2 or every 3 weeks, and there's no difference in efficacy.

I'm going to ask Dr. Abramson to speak to the intervals of 2 or 3 weeks to that, and then we'll move on to the other parts.

Dr. Abramson, do you want to quickly address that with regard to 2 versus 3 weeks in lymphoma?

DR. ABRAMSON: Sure. R-GemOx has been administered at either 2-week or every 3-week intervals. From a practical perspective, 3-week intervals in this study allowed alignment with the Glofit dosing schedule, and therefore it made sense.

I will refer back to a comment in the FDA presentation that it's often administered every 2 weeks because of the aggressive nature of the disease. I would note that isn't necessarily the rationale for the schedule of R-GemOx. And, in fact, the majority of lymphoma regimens for diffuse large B-cell lymphoma most notably R-CHOP. The

most widely used regimen in the world for DLBCL is administered at a 3-week interval, not at a 2-week interval, and a randomized trial in that setting showed no benefit to dose-dense administration. So 3 weeks is a standard interval for treatment for DLBCL.

DR. FUCHS: Then moving on to your other question, Dr. Nooka, I'm going to invite Dr. Kesavan, who was the medical director for STARGLO. I actually want to ask him to do it in the context, perhaps, of the discussion that our colleagues of the FDA made, and it really points to actually including discontinuation, table 19 of the briefing document.

So, I'm going to ask Dr. Kesavan to address that point, as well as the related points that you mentioned in the context of the discontinuation of R-GemOx by region, as well as the other factors identified in table 19 by our colleagues.

DR. KESAVAN: Murali Kesavan, Genentech. I'm a hematologist, and medical director, and medical monitor on this study. I think it's a very

important question, Dr. Nooka, but I think it's in the broader context, and it would be important for us to understand. The overall question about applicability, I think it's important to emphasize some of the points.

Just to highlight, I'll bring up table 19.

DR. FUCHS: Well, it looks like we still have the FDA slide. Thank you.

DR. KESAVAN: These are the points, and you'll see in the bottom section are the treatments and assessments. I think we'll just go through these quickly. These are all things that we noticed when we both were designing the study. We take into account baseline characteristics and treatments, but also when looking at the study results; so just to highlight them here today for your benefit and to help your understanding of our analysis, and obviously inform your very important discussion.

The first thing is regarding the differential treatment. As you heard from Dr. Sethuraman, NALT did have a preferential impact

in the R-GemOx control arm in North America, Australia, and Europe. And when we controlled for that, we did see -- and I think this is important -- a consistent benefit across OS, PFS, and EFS to a hazard ratio less than 1.

In terms of patient- and disease-related factors, a number of these things were brought up. We obviously showed you the MVA, which took into account all of those, but it's important to highlight that a lot of these factors have limited prognostic impact in the relapsed/refractory DLBCL setting, so that was already considered.

In particular, cell of origin is not considered prognostic in relapse, and some of the data shared by our colleagues from the FDA was referring to patients who underwent stem cell transplantation. So with standard chemoimmunotherapy, cell of origin is not prognostic in the relapsed setting. And again, in terms of transplant refusal, only 10 percent of the patients, based on standardized criteria, refused stem cell transplant, and that number is also

reflective of patients who refused in the U.S.

I think this is the important bit, getting to your point, Dr. Nooka. All patients were managed as per clinical need and standard of care guidance on this study, and that standard of care guidance is globally completely aligned.

Patients who were treated on the R-GemOx Asian cohort, there was a slightly higher proportion of early relapsing patients who often present with aggressive disease, and those patients are more likely to experience symptoms of treatment failure, which was the case here. They're more likely to need early treatment assessment, which was the case here. And they're more likely to have to discontinue from treatment. And that bears out in this cohort, and what we see is that there's an exceptionally high concordance between investigators in the IRC confirming those progressions, and indeed confirming the lack of efficacy as well.

In response specifically to your question around GemOx and the discontinuations, we don't

have data to share specifically around the GemOx backbone discontinuations, but what we know is across both arms, the control and in the intervention arm, discontinuations were primarily driven by a lack of efficacy or progressive disease. And where progressive disease was identified by the investigator, there was exceptionally high concordance with the IRC.

Then the last point around utilization, I think going back to Dr. Lieu's point is that at the time of this study, all regions represented had the same access to therapies, including CAR T and bispecifics. And, obviously, application was variable but primarily driven by patient need, as you would expect.

DR. VASAN: FDA, would you like to respond?

DR. SUNSERI: This is Nicole Sunseri with the FDA. In terms of the regional discontinuations, I don't have a slide for it, but we did do that analysis, and there were more discontinuations in the non-Asian region versus the Asian. To be specific, for the R-GemOx arm,

19 percent versus 7 percent, with the 19 percent being the non-Asian. Glofit-GemOx was 18 percent versus 12 percent, 18 percent being the non-Asian.

DR. FUCHS: And just to clarify, 70 percent of patients who discontinued R-GemOx in Asia did so for progression or death.

DR. VASAN: Neil Vasan. I had a question, just drilling down to the transplant ineligibility numbers. There's a discrepancy between what the FDA is calling transplant ineligibility from a patient refusal point of view to what the company is saying.

This is slide 69 of the FDA packet. The FDA said that 95 total patients refused transplant, corresponding to 65 percent of the population, whereas the company has said 29 total patients, corresponding to 11 percent, and the speaker just referenced this before. So I'm just trying to understand what is the reason for this very large discrepant analysis.

And a follow-up question to that is also if the applicant has conducted a sensitivity analysis,

excluding patients whose transplant ineligibility was based solely on refusal?

DR. FUCHS: Yes. I'm going to ask Dr. Kesavan to come back to the podium, Dr. Vasan, because I think it is important to understand this discrepancy, and I'll let him describe that.

DR. KESAVAN: Murali Kesavan, Genentech. I think this is a very important point that you raise, Dr. Vasan, and we want to be very clear.

I think there's a little bit of context required here. When transplant is indicated in the relapsed/refractory DLBCL setting, as outlined in the talk by Dr. Abramson, it's considered standard of care in the second-line setting for patients. So outside of that second-line setting, it's really not considered the optimal treatment choice for patients.

The second thing just to briefly touch upon, the process of transplantation really is driving at trying to control someone's aggressive disease with very high-dose chemotherapy, as many people on the panel would know. So it's not always the right

choice of treatment for patients who are experiencing early relapse or chemorefractory disease.

In addition to the primary reasons collected for transplant eligibility in our study, we also collected secondary and other reasons looking at medical comorbidities and age, and these were all standardized criteria applied in the study, so all patients were not candidates for transplant. And I'll share our slide. I think the FDA slides are still projecting.

So, when we think about those standardized criteria -- so, age, comorbidities, renal function, and functional status -- and also think about the line of therapy and apply them to those 95 patients where refusal was identified as one of the reasons, what we find, as pointed out by Dr. Boyer, is, ultimately, there are 29 patients included in the study where refusal was the sole and only reason for non-candidacy for transplantation. And when we do a sensitivity analysis excluding these 29 patients, what we find is that the overall

efficacy results of the study are maintained.

This is of the 95 patients, so we find the same results when we do a sensitivity analysis with the 95. And then I'll show you slide 4, and we find the same outcome when we do a sensitivity analysis with the 29 patients. But ultimately, the patients that were not considered candidates based on refusal were representative of 10 percent, and that's reflective of real-world data where we see a similar refusal rate.

DR. VASAN: Could FDA respond to this analysis?

DR. RICHARDSON: Thank you, Dr. Vasan. Nicholas Richardson, FDA.

So again, this was an important component that was raised as one of the multiple factors that were identified that signaled that there may be distinctions between the populations based on region. So, one of the main reasons for the FDA to highlight patient refusal as an eligibility criterion for transplant is that it is challenging to characterize who those patients are because the

patient refusal is a subjective measure compared to other objective measures such as age and comorbidities.

Again, the STARGLO trial, the intended population really were those that were ineligible for transplant. Acknowledge that in the second-line setting, the first determination is whether a patient is suitable for CAR T-cell therapy or to pursue high dose therapy followed by transplant. Transplant is utilized less frequently in the third-line and beyond setting, only for select patients likely on a patient provider discussion.

So, just to really get back to the point, it really challenges the ability to characterize the patient population. And when we see an imbalance like that in the inability to use objective measures to characterize that population, it really raises uncertainty in how that population is reflective of the U.S. population.

Additionally, when we analyze the STARGLO data, the eligibility criterion and the reasons for

transplant ineligibility that were shown in the FDA presentation were what were provided by the applicant, in addition to what was provided in the data sets. So it is helpful to hear the additional information regarding some of the characterization of these patients.

DR. VASAN: Thank you.

Dr. Conaway?

DR. CONAWAY: Mark Conaway, University of Virginia, and this question is for Dr. Sethuraman, please.

I was looking at figure 9 on page 40 of the combined briefing document, and even though you showed that doing the inverse probability weighting for NALT enhanced the treatment effect --it drove the hazard ratio of less than 1 for both -- you still see a differential treatment effect by region. The hazard ratio is like 0.6 in the non-Asian region and about 0.3, and those look statistically different.

So, my question is, in all the analyses you did, were there any that made that, essentially,

treatment by region interaction disappear? Because even with the NALT analysis, it seems like it retains that differential treatment effect.

DR. FUCHS: Well, Dr. Conway, let me invite Dr. Sethuraman to come up to answer your question.

DR. SETHURAMAN: Venkat Sethuraman, Genentech. Thank you for your question. I'll answer the first part of the question regarding the differential treatment we still observe.

I do acknowledge there is a differential treatment that we still see between these two aspects of it. One way, FDA also acknowledges this aspect around interaction test as a way to formally test whether there is any difference in here, so acknowledging that there is a lot of multiplicity involved in this, and we did do an interaction test after doing IPCW adjustment. Let me bring up the slide.

If you do the multiplicity adjustment after -- if you do the IPCW adjustment for this particular OS, you see that there is no interaction effect, almost goes away. So 0.3 and 0.62 no

longer looks significant. Thank you.

DR. VASAN: The FDA would like to respond?

DR. RICHARDSON: Nicholas Richardson, FDA. Can I ask our FDA statistical colleagues to respond?

DR. WANG: This is Shu Wang, statistical reviewer, FDA. Can we pull up FDA backup slide number 143, please? Thank you.

Thank you for the question. We just want to clarify that regarding IPCW, we want to mention, in the context of STARGLO, the general purpose is to estimate the alternative treatment effect, and there's a hypothetical scenario in which NALT does not exist. And as listed here, there are several limitations of IPCW. Then we want to emphasize the last point. IPCW was not prespecified in STARGLO; therefore, the selection of the prognostic factors in the model of IPCW are post hoc.

Also, we want to emphasize that in the context of STARGLO, IPCW may not be relevant. As mentioned, IPCW wants to estimate treatment effect assuming NALT does not exist; however, as we

discussed, NALTs are realistic parts of patients' treatment pathway for the relapsed/refractory DLBCL patients; therefore, the FDA believes that NALT should be captured in the assessment of OS, which means that we would want to estimate the treatment effect in the presence of NALT rather than trying to remove them.

Can we go to next slide, please?

Also, I want to address the committee's question. If we look at the second point, the selection of prognostic factors are post hoc, actually, we found that the IPCW results are highly dependent on what factors we selected and included in the model. So just for OS results, if we try different covariate sets, and we put them in the IPCW, we can get a wide range of results for ITT for Asian region and non-Asian region, respectively.

So, you may get very good results indicating a huge treatment effect and you may also get a treatment effect, for example, for non-Asian region, as high as a 1.05 regarding the hazard

ratio. Therefore, we believe that in the context of STARGLO, the IPCW result is exploratory only. Also, lastly, we still want to emphasize we believe this analysis is not as relevant in the context of the STARGLO study. Thank you.

DR. FUCHS: Dr. Vasan, can I just respond? Because I wasn't aware of these additional analyses by the FDA.

DR. VASAN: Yes.

DR. FUCHS: I think the comment -- and I'm going to ask Dr. Sethuraman to return -- of this being post hoc, we're here looking at post hoc analyses. The study delivered a 41 percent improvement in overall survival, and that was the predefined endpoint of STARGLO in overall survival. We're obviously looking at subgroups, and we should because we owe it to patients to vet those subgroups, but all of what we're doing is post hoc. The IPCW is simply to try to understand that particular subgroup.

I'll let Dr. Sethuraman provide some additional context there.

DR. SETHURAMAN: Venkat Sethuraman, Genentech. I want to bring up a slide to address the comment that FDA colleagues made.

First and foremost, we all acknowledge that it is a post hoc analysis that we have done. We formally had a very prespecified approach in terms of model selection, as well as variable selection. So, first, we had 26 prespecified baseline factors that were identified. We did them using univariate analysis with a prespecified threshold for selecting these factors. Then, we also looked at the multicollinearity.

According to the comment made earlier, of course we understand picking up these factors could influence the way of outcomes, but we went through a very formal approach in terms of identifying the key factor that is required. Once we took those factors into account, we identified six of them that was applied into the IPCW approach.

Then the most important question we are answering is two types of estimands. One estimand is where we are looking at the treatment policy or

the ITT, where we are trying to estimate the overall survival effect in presence of study treatment, as well as subsequent therapy; so that we all know. The second is an hypothetical scenario, the scenario, which we don't know, where we need to estimate OS in the absence of NALT. And that's the question we are trying to answer through the IPCW approach.

There are multiple approaches in here that we can do in terms of estimating what is the true treatment effect in the absence of it, so we went through a rigorous approach, and then we identified that if you adjust for IPCW, the OS estimates are very much consistent with the ITT population. Thank you.

DR. VASAN: Alright. There are multiple other questions that the standing members have, but right now we will take a 10-minute break. We will return to additional clarifying questions at the end of the OPH session.

Panel members, please remember that there should be no discussion of the meeting topic during

the break amongst yourselves or with any member of the audience, and we will resume at 10:37.

(Whereupon, at 10:27 a.m., a recess was taken, and meeting resumed at 10:38 a.m.)

Open Public Hearing

DR. VASAN: Welcome back. 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 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 you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the industry group. For example, this financial information may include the industry group's payment of your travel, lodging, or other expenses in connection with your participation in

the meeting.

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

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

For those presenting virtually, please remember to unmute and turn on your camera when the OPH number is called. For those presenting in

person, please step up to the podium when your OPH number is called. As a reminder, please speak only when recognized by the chairperson. Thank you for your cooperation.

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

DR. BERHAUPT: Good morning. My name is Amanda Berhaupt. I'm the Health Policy Director for the National Center for Health Research. We are a non-profit think tank that evaluates scientific evidence on the safety and efficacy of drugs, biologics, and medical devices. We do not accept funding from any entities with a financial interest in our work, so we have no conflicts of interest to report.

I am a proud FDA alumna, and I appreciate the chance to share NCHR's concerns about the STARGLO confirmatory trial at this important meeting. As you are well aware, STARGLO is a randomized trial of 274 patients in four regions: 25 U.S. patients; 88 in Europe across 9 countries;

30 in Australia; and 131 across China, Korea, and Taiwan. As you also know, one group received a drug combination including glofitamab, while the second group received a combination that substituted glofitamab with rituximab. All patients had at least one unsuccessful prior line of systemic therapy and were ineligible for stem cell transplantation.

STARGLO results demonstrated a statistically significant improvement in overall survival, progression-free survival, and complete response rate in the group receiving the glofitamab drug combination compared to the other group. However, the overall survival was lower for patients living in the U.S. and Europe than in China, Korea, and Taiwan. White patients, regardless of where they lived, were significantly less likely to survive than Asian patients, and the same was true for the secondary endpoints as well.

As you just heard, the FDA described these results as inconsistent and raised concern about the robustness of the efficacy and safety data, and

whether these results could be generalized to U.S. patient population. To address this, the agency completed the subgroup analysis, merging patients into two groups, those residing in an Asian region and others outside of an Asian region.

While regrouping led to a balanced sample size to compare results for patients in the Asian and non-Asian regions, only 9 percent, that's 25 patients in the study, were actually based in the U.S. for a trial seeking drug approval for use in the U.S. patient population. This means there were only 15 U.S. patients in the glofitamab drug combination group and 10 in the other group.

A key question is why patients in Asia benefited from the glofitamab drug combination, while patients in the U.S., Europe, and Australia did not. There are several factors that were identified earlier. The U.S. patients were older and were different in terms of their health and our healthcare system. For the most, Asian patients were younger than 65 years old compared with non-Asians who were older. And while the study

intended to include patients who were ineligible for transplants, 65 percent of patients in the Asian region refused a transplant, whereas in the U.S., 60 percent of ineligibility was due to an age limitation.

There were also regional differences in the type of therapies used by Asian patients versus others, as was the cell of origin. Furthermore, more Asian patients also discontinued treatment due to progressive disease. The bottom line is that patients studied in Asia benefited from the drug combination under consideration this morning, but the other patients did not.

NCHR applauds the FDA for completing the subgroup analysis. The agency's main focus is to study treatments for U.S. patients, and the STARGLO trial did not confirm the benefits identified during the accelerated approval of glofitamab. Moreover, there were potential safety concerns for cytokine release syndrome, infection, neurologic toxicity, and tumor flare.

The study results are not merely

inconsistent, but rather they indicate a lack of benefit for U.S. patients for the indications specified, and therefore do not meet the standard for patients, nor the standard for oncological medical care in the United States. Thank you.

DR. VASAN: Thank you.

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

MS. SEKONI: Good morning. My name is Daneen Sekoni, Vice President of Policy and Advocacy at Cancer Support Community. Cancer Support Community is an international non-profit organization that provides support, education, and hope to those affected by cancer. As the largest provider of social and emotional support services for people impacted by cancer, we have a unique understanding of the cancer patient experience and have learned a great deal from those we support.

Thank you for the opportunity to be here today to provide comments regarding approval of the supplemental biologics license application for

glofitamab, for treatment of adults with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, who are not candidates for autologous stem cell transplant. While CSC does not endorse any specific product, we do encourage, when appropriate, the development and approval of effective treatments that give more options to patients, especially those that specifically improve treatment access and adherence.

We provide services to people with aggressive blood cancer such as diffuse large B-cell lymphoma. There are many barriers to care for these patients, as many patients are not candidates for auto stem cell transplants and are unable to access CAR T, often for logistical reasons like travel, lack of family caregivers, and financial toxicity. Having an additional treatment option available could greatly increase access to care for these patients, particularly in the community setting.

I will now highlight patients' stories from our helpline and findings from a recent study we

conducted on barriers to CAR T in the community for patients and caregivers. These are also very similar issues, with the exception of insurance requirements that patients face with auto stem cell as well.

Our study found that lack of caregiver support is one of the reasons that patients considered refusing CAR T. Our helpline recently provided support for a single woman in her 60s, never married, with no children, who was diagnosed with lymphoma, and her oncologist is recommending CAR T. However, she is currently the caregiver for her elderly mother who has dementia and has moved into her mother's house to care for her. For these reasons, she decided that she could not receive CAR T because she does not have a caregiver and does not have the funds to pay for a caregiver for herself while she's receiving CAR T and a caregiver for her mother.

Distance from treatment centers can restrict patient access to CAR T therapies, as well as their willingness to pursue the treatment. One study

found that the likelihood of receiving CAR T was reduced by 40 percent when patients live 2 to 4 hours from the nearest treatment center, in part, due to the considerable time, logistical, and financial burdens. In some cases, these logistical burdens prevent providers from referring people for CAR T.

One patient who recently participated in our focus group shared that multiple family members traveled 2,000 miles to stay with her during the 4 weeks following CAR T, exhausting their FMLA and PTO and spending thousands on travel. Insurance companies may require patients receive CAR T at centers with special accreditation and extensive medical justification, causing significant delays in accessing care.

A caregiver of a CAR T patient who participated in our focus group shared that their insurance required them to travel to a CAR T center 2 and a half hours away, which created a significant financial and logistical burden for the family who was forced into early retirement.

I also want to point out that not all patient populations for which CAR T may be appropriate are given the option. While Cancer Support Community and others are doing work to increase access to CAR T in the community, we know that most CAR T authorized treatment centers are academic institutions, and these centers remain out of reach to many patients, especially those in rural communities.

In addition, a 2024 ADVI analysis found disparities in CAR T therapy access for Black, Medicare fee for service, and Medicare Advantage beneficiaries diagnosed with blood cancers despite living closer to qualified centers.

In closing, Cancer Support Community recommends that patients in the community who choose not to leave their medical home, whether for personal preferences regarding the risk of side effects, financial, social support, logistical, lack of required caregivers, or other reasons, be able to have additional options for treatment. Thank you.

Clarifying Questions (continued)

DR. VASAN: Thank you.

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

As we have additional time, we'll now take remaining clarifying questions. 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 that, if possible. And as a gentle reminder, please acknowledge the end of your question with a thank you and end your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Next, I have Dr. Frenkl.

DR. FRENKL: Thanks very much. Tara Frenkl, industry representative. This is a question probably for either Dr. Abramson or Dr. Patel.

I note the large difference in the control arm by region in terms of efficacy, with 8 months

in the Asia region versus over 20 months in the North American, EU, and Australian region. And the Asia 12 months is more consistent with what is historically seen in the literature, so I can only assume that this is impacted by the NALT.

So, I'd really like to understand the applicability of the NALT from the Asian region that was used to the general population in the U.S. As we just heard from this public speaker, not everyone has access, I think, to the higher efficacy NALT that was used in the study.

Is that clear?

DR. FUCHS: It is, Dr. Frenkl. Thank you. I'm going to invite, actually, both Dr. Patel and Dr. Abdulhaq to answer your question, specifically around the application of NALT, and as you rightly point out, the survival that was larger in the R-GemOx arm of roughly 28 months in Europe, North America, and Australia. I'll let Dr. Patel start. As well, he can speak to just the interpretation as well.

DR. FRENKL: Thank you.

DR. PATEL: Krish Patel, SCRI. Thank you, Dr. Frenkl, for the question. I think it's an important observation. I think the agency highlighted many characteristics of Asian patients that might be different, but I would emphasize, actually, that most U.S. patients look very much like the patients in Asia, including the patients who, ultimately, may not have access to highly effective NALT like CAR T-cell therapy.

I practiced for many years in Seattle, Washington. In the northwest, we served 15 million lives. The story that was shared by a patient advocacy group, it really resonates. We have numbers of patients who are never able to reach the CAR T center and never able to access those therapies. So very much, we do see patients in the U.S. who are younger, have primary refractory disease, who refuse, due to logistical factors, therapies like highly effective NALT that will never be a reality for them.

So I think this is a really important question you raise and really highlights the unmet

need we have in the U.S. The U.S. population looks very much like the Asian population in practice.

DR. FRENKL: Thank you.

DR. ABDULHAQ: Haifaa Abdulhaq, Director of Hematology at UCSF Fresno. I'm investigator on the STARGLO study and I'm consultant for Genentech. I would like also to reiterate that on the STARGLO study, centers in the U.S. had access to transplant, and they were mainly academic centers. There were very few community centers on the STARGLO trial.

These patients did have access to the new NALT therapy, including CAR T; however, what I would like to emphasize is that in the community, like, for example, where I work in Fresno in the Central Valley of California, we do not have CAR T as of now. We don't have any CAR T centers. We do treat diverse patient populations, and there is a significant unmet need in the patients in the second-line setting of relapsed/refractory diffuse large B-cell lymphoma for effective and immediate treatments that can be given to these patients,

especially when they have rapid progression of their disease for treatments to be effective and to be given close to home.

I've treated many patients with Glofit-GemOx, and one patient comes to mind. She's 78 years old who had relapsed lymphoma after first-line chemoimmunotherapy. She relapsed after 10 months, and her only caregiver was her daughter. At the same time, her husband was diagnosed with prostate cancer, and the daughter was the main caregiver. And for her, travel was not an option. I chose to treat her with Glofit-GemOx. She finished her treatment in January, and she achieved a CR. She's very grateful that she was able to be treated close to home. She is in CR, and she was able also to care for her husband.

This is just one example. This case is not unique. We treat diverse patient populations in the community, and they are in need of these effective treatments. So I just believe that Glofit-GemOx is an important treatment regimen for our patients, as it results in durable CRs. Thank

you.

DR. FRENKL: Thank you.

DR. VASAN: Thanks. Would the FDA like to respond?

DR. GORMLEY: Yes, the FDA would like to respond. This is Nicole Gormley, FDA, DHM II. Two comments, and I'm going to ask perhaps we can work on pulling up FDA backup slides in just a moment as well.

Two comments. The first, I just really want to reiterate that this is not an advisory committee meeting regarding CAR T therapies. We're really here to assess whether or not the results of STARGLO are applicable to a U.S. patient population. I think we can all recognize in this cancer, and others, there's always a need for more effective therapies, so that goes without saying.

The second item I wanted to address regarding, Dr. Frenkl, your comments was you really seem to be hinting at what's putting the results of R-GemOx in context, and you referred to the sponsor's slide regarding overall survival. I

would just like to highlight that in many regards, this sort of line of questioning is really challenging and fraught with some limitations; that it inherently relies on cross -trial comparisons, which are fraught with many challenges and bias interpretation as well.

So, in general, we should be able to rely on the results from within the trial because that's controlled by randomization. And if we have to rely on external data to interpret the trial, that really calls into question the robustness and interpretability of that trial itself. If external data is needed, it really suggests that the clinical trial may not meet the standard of an adequate, well-controlled trial.

The other aspect, we did look at this at the FDA to put this into context, despite the limitations of doing cross-trial comparisons. We looked at this, though, however -- and perhaps you can pull up slide 109, and I'll allow Dr. Sunseri to comment. But we looked at this in terms of response rate data from the literature. OS, as

we've been discussing, can be impacted by multiple things: subsequent therapy, other supportive care in the region, just different practices, so we felt like looking at response rate, and CR in particular, would provide a little bit more of an unbiased assessment of this.

If you could pull up FDA slide 109, and I'll allow Dr. Sunseri to comment.

DR. SUNSERI: This is Nicole Sunseri with FDA. This is a look at the real-world data and the literature for R-GemOx based on the response rate, so ORR and CR, and the very top portions in white, and then how it compares to STARGLO's population, the ITT as well as by Asian and non-Asian regions.

And as you can see, the range, particularly for CR, can be from 20 to up to 58 percent, so that inherent variability goes for when you're looking at cross-trial comparisons, the issues with that. But just taking that as it is, when you look at the STARGLO Asian results, 17 percent versus the non-Asian at 34 percent, it's actually more suggestive of -- it's hard to say, but like a lower

performance in the Asian, but the non-Asian is more on par with what you would expect, based on the response rate.

For the reasons that Dr. Gormley mentioned, we've looked at response rate as opposed to PFS and OS because of the potential issues that are even more confounded in the setting of looking at cross-trial comparisons.

DR. FUCHS: Dr. Vasan, can I respond to that now?

DR. VASAN: Yes.

DR. FUCHS: Yes. I totally agree that cross-trial comparisons are fraught, but if we're going to do it, we want to use endpoints that are incontrovertible. I would suggest that as compared to assessed response, that mortality is an indisputable endpoint.

If we could bring up the slide from Dr. Sethuraman's presentation on the comparison of R-GemOx performance, these are the median survivals for R-GemOx studies that were contemporaneous in Asia, in the U.S., and across the world. And as

you can see, the R-GemOx in the ITT performed at overall survival, the primary endpoint of the study, consistent with that range of 8 to 13.5 months; Asia came in at 8.2 consistent; and North America, Europe, and Australia came in at 27.8 months. Obviously, that's an outlier.

As you heard from Dr. Sethuraman, it's driven by the application of NALT, and NALT applied not only at the time of progression but, frankly, prior to it because objective response, partial response, is not an endpoint that is acceptable in the context of lymphoma care. It's complete response that needs to be achieved because CR is a path to cure.

But with regard to agree -- and you can take the slide down -- I agree with Dr. Gormley that this should really be about the data that STARGLO does provide as it compared to cross-trial comparison. The study is a multiregional study intended to provide global evidence to assess the effect of Glofit-GemOx in overall survival, and it delivered that with a 41 percent improvement in

survival.

I just want to leave you with four points as you contemplate applicability. One, you've heard there is no biologic or clinical evidence, I think, as you heard from the experts, that this disease is different or the treatment effect is different across regions of the world; two, that glofitamab's PK profile, safety and efficacy were absolutely consistent across the globe; that actually in our trial, when you look at the performance of Glofit-GemOx, the intervention arm for which we seek FDA approval, the impact on survival was absolutely consistent across the world, North America, Europe, Australia and Asia. And then finally, as you heard from Dr. Patel, if you look at the characteristics of the population enrolled in the ITT population of STARGLO, it is consistent with the U.S. population.

So I realize and I appreciate, Dr. Gormley, that the question for the day is, in fact, applicability. And I would ask you to consider those four points, as well as the fact that this

trial met its intended endpoint of survival.

Thank you, Dr. Vasan, for letting me respond.

DR. VASAN: Alright. We have two more clarifying questions, one from Dr. Choueiri.

DR. CHOUEIRI: Hello, everyone. Thank you for having me today. My question is, I heard opposing views on the cell of origin in lymphoma from Professor Abramson, and as well from the FDA, and the effect on this disease. I would like to know if this is prognostic or not because I heard differing views. Thank you.

DR. FUCHS: I could invite Dr. Abramson to present some additional data in the context of relapsed/refractory, Dr. Choueiri, if that would help; sure.

Dr. Abramson?

DR. CHOUEIRI: That would be perfect.

DR. ABRAMSON: Jeremy Abramson, Mass General. The prognostic impact of cell of origin is really entirely applicable to frontline chemoimmunotherapy rather than subsequent lines of

therapy. Furthermore, if we look at the options that were demonstrated in the FDA slide that suggested differential impact of cell of origin in the relapsed/refractory setting, neither one is applicable to the STARGLO population. The DHAP regimen was cited based on a post hoc analysis, which is not applicable to a non-transplant eligible DLBCL population, and the other regimen of bortezomib-based treatment is an upfront chemoimmunotherapy that is not approved and has no usage whatsoever in the United States.

And so, not a single prospective trial or standard approved regimen for relapsed DLBCL has any impact of cell of origin and treatment selection, nor, as you can see on multiple studies shown on the slide in front of you --

DR. FUCHS: We can see Dr. Choueiri, but we can't see the slide.

DR. ABRAMSON: It's behind us.

DR. FUCHS: Oh, you can see it.

DR. ABRAMSON: So you can see on multiple analyses that have looked at R-GemOx, and

specifically non-transplant eligible population, that there is no prognostic impact of cell of origin on relapsed/refractory outcomes in diffuse large B-cell lymphoma.

DR. VASAN: Thank you.

Would the FDA like to respond?

DR. CHOUEIRI: Thank you. I'm satisfied.

DR. MERINO: Margret Merino, FDA. Regarding the cell of origin, I think there are a couple big points to make here. One is, the question of cell of origin and its prognostic significance in the relapsed/refractory setting I think is an unknown versus that there is no relevance.

I wish that we had better data from the STARGLO trial about cell of origin because I think this is an important issue, particularly when we also have data supporting the difference in racial and regions, and that there there may be a difference at least in several reported studies.

It is fairly common to have cell of origin, at least some level, when we are looking at these registrational trials in lymphoma. Often that is

complicated because you have the cell of origin classification, as well as the methods of classification. But it is common that we see, actually, stratification for cell of origin even in trials in relapsed/refractory setting. We also, not infrequently, have trials that are evaluating patients in a particular cell of origin subtype based on a mechanism of action.

So I would agree that it's not clear, but there is data to support, in the upfront setting, correlation with poor prognostic ABC subtype with overall survival. It is an evolving field. It's very nuanced, and it's important information to consider in the setting, especially given what we know about the regional differences.

DR. VASAN: The last clarifying question is from Dr. Madan.

DR. MADAN: Ravi Madan, National Cancer Institute. This question is for the sponsor; if they can share the rationale for having a minimum patient accrual for China and Taiwan but not any other region.

DR. FUCHS: Dr. Madan, thank you for asking that question. There was no minimum Asian-Chinese enrollment. We had conversations with health authorities across the globe. That includes the European Union, as well as China. In the conversations with China, they stipulated that they needed to see data in a subset of patients. I actually think it was less than 80. What we decided was that -- and it says it in the document that was shown -- if we don't enroll 80 patients in STARGLO, we would enroll additional Chinese patients as a part of an an extension cohort, as is often done when you submit to Chinese health authorities. What we did operationally is we stopped enrollment in China, in Asia rather, at 80 because we wanted to ensure that there was additional enrollment outside of that region.

An important point of what happened in North America and Europe, it was the pandemic. The study opened in 2020 when the pandemic happened. Like many of you, I was running a cancer center in 2020. I shut down, as did many of my colleagues, cancer

centers. I closed clinical research at Yale, and it took us a long time to reopen it. And even when we reopened it, we opened three trials a week initially because we couldn't bring our CRAs on site.

So when we saw to enroll in U.S., we had difficulty. The most sites of any country was the U.S. As you heard, the reason we extended our analysis beyond the interim analysis, that showed a 41 percent improvement in survival, was because we still had patients on treatment, and we thought it was important to get additional follow-up, particularly from those regions of the world that were enrolling later.

What we found was still a consistent benefit of overall survival. We still saw roughly a 40 percent improvement in overall survival, but we did not stipulate a minimum of 80 patients in STARGLO. We agreed that we would need to have 80 patients ultimately for Chinese submission. And if those 80 didn't exist in STARGLO, they would be enrolled in an extension cohort as part of our

submission to China. I think it's important to get that point across because it's mentioned more than once by our colleagues in the briefing document. And obviously today that is not the case. We did not say there needs to be a minimum 80 in STARGLO

DR. VASAN: Would the FDA like to respond?

DR. PAZDUR: I just have a question. I want to make it very clear, your statement, if you could clarify it. The Chinese government did not request 80 patients. You agreed to that or this was a Genentech enrollment.

DR. FUCHS: My recollection, Dr. Pazdur, was the number that the Chinese asked for was less than 80. We had decided, as part of our ultimate submission to China, that we would have data on 80 patients, which would include STARGLO, as well as an extension cohort for China.

DR. PAZDUR: Why did you do that?

DR. FUCHS: Why did we choose 80? Because we just wanted to make sure that beyond whatever STARGLO could contribute, that we would have --

DR. PAZDUR: And what was the minimum

requirement that the Chinese government wanted?

DR. FUCHS: You know, I'm going to perhaps ask Dr. Weber, if I may. Forgive me.

Dr. Weber, if you would like to just speak to who led the regulatory component, to speak to that.

DR. WEBER: Ashley Weber with Genentech.

Dr. Pazdur, to answer your question, the Chinese Health Authority had provided feedback relevant to a target percentage as to what we should enroll, so, operationally, Genentech had chose to have up to 80 patients.

DR. PAZDUR: And what was that target that they wanted? The Chinese government, you just said, had a target enrollment. What was that target that the Chinese government wanted?

DR. WEBER: I believe approximately 15 percent was the target enrollment; however, it was a bit of --

DR. PAZDUR: Thirty percent.

DR. WEBER: Which is, ultimately, the case of being able to cap the enrollment in Asia,

operationally, to allow for a multiregional clinical trial to enroll for other regions.

DR. FUCHS: Honestly, Dr. Pazdur, my recollection is it was somewhere in the range of 45 patients that they wanted to see data on. Because we were able to robustly enroll in Asia during the pandemic, we then capped at 80 to ensure enrollment of the other sites.

I will say that we also think it's important to have robust data in the U.S. We have two ongoing phase 1b extension studies in the U.S. One's of Glofit-GemOx, one in underserved minorities for whom we want to make sure we get data. The other is a study looking at the use/ delivery of this regimen in an outpatient setting, and we look forward to presenting both of those studies to you when those ongoing studies are completed in the U.S.

DR. PAZDUR: Being somewhat of a skeptical person, if you had a goal of 80 patients, you would probably want to push enrollment in China. Was that the situation or am I misreading this?

DR. FUCHS: No, sir. Literally it was we couldn't enroll patients in the U.S. and Europe during the early part of the study enrollment because of the pandemic, and Asia was enrolling robustly. So when we hit 80, we stopped.

DR. PAZDUR: And what efforts did you entertain to increase the enrollment? Obviously, you had additional sites, but why weren't these sites enrolling patients?

DR. FUCHS: In the U.S., yes, because, as I told you, I think we were hampered initially in 2020 and '21. Again, at the risk of repeating myself, when I was at Yale, we stopped enrollment. We were running probably about 350 studies across our cancer center. Even when we restarted in the latter part of 2020, we were only enrolling, opening, a handful of studies every week so that we had the capacity to manage it.

That phenomenon, when I was having calls with my fellow cancer center directors, we were having a similar phenomenon. That was really what was driving our issue at Genentech in the early

part of STARGLO enrollment. Realizing that we did want to make sure we had a global population, that's why we said at 80 we're stopping. And moreover, even though we hit the hazard ratio of 0.59 at the interim, and the IDMC said this is now your final, we elected, as you know, to continue follow-up for an additional 9 months because we had patients on therapy as part of the later enrollments, and we wanted to make sure that we gathered more data.

DR. PAZDUR: So you're feeling that this was a COVID phenomenon that prevented the U.S. enrollment from increasing.

DR. FUCHS: Principally, yes.

DR. PAZDUR: And if my recollection is correct, wasn't China closed very early and for a longer period of time than the United States?

DR. FUCHS: I can assure you those patients --

DR. PAZDUR: The society in general I'm talking about.

DR. FUCHS: So, yes. If you talk to

colleagues, those who were not involved in health care were locked down. I can't really speak in detail; I just know third hand. But the evidence is clear they were enrolling patients. I mean, you can look at when these people were enrolled in Asia, in China; they were being enrolled at that period of time. We just couldn't do it in the U.S. and Europe at the time. And I can only speak for my personal --

DR. PAZDUR: A problem with the control arm was given. It was truly --

DR. FUCHS: No. It was simply that we -- because, obviously, you know, when you enroll a patient, you don't know which arm they're going to go on until the randomization is completed. We simply couldn't enroll in the U.S. And frankly, for a very long period of time in my own cancer center, we weren't enrolling anyone on a clinical trial.

Questions to the Committee and Discussion

DR. VASAN: Alright. Thank you.

The committee will now turn its attention to

address the task at hand, the careful consideration of the data for the committee, as well as the public comments. We'll 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. After I read each question, we will pause for any questions or comments concerning its wording. Slide 2, please.

We will proceed with our first question, which is a discussion question. Discuss how the differential results observed in the Asian and non-Asian regions impact the overall interpretation of the STARGLO trial results and the generalizability to a U.S. population.

Are there any issues or questions about the wording?

(No response.)

DR. VASAN: Great.

And I just want to reiterate that the discussion point, the FDA is not seeking the advice

of the committee as to whether STARGLO should be used to convert the accelerated approval to the traditional approval; rather, we're discussing this question here.

Are there any points? Dr. Nooka?

DR. NOOKA: I'll start. The major randomized phase 3 trial with a primary endpoint of overall survival is a good study design that has led to -- fully understanding that's not the question -- a hazard ratio of 0.6, a 40 percent reduction in the risk of death.

What is clear here is there's 9 percent U.S. population that we are seeing, and this should be an eye-opener for all of us in the future to start with a representative patient population to be included in the clinical trials. What I struggle with is the small sample size of 25 patients, allowing us to make decisions when there is no stratification that was, a priori, designed by the region. So, there is a likelihood of an imbalance in the arms in the regions between the Glofit-GemOx versus R-GemOx. And clearly what we're seeing here

is an enrichment of the high-risk patient population in these 25 patients and the Glofit-GemOx arm.

So, to generalize these specific results of what we're seeing in the trial to the generalized look at the U.S. patient population, I believe it is a little premature, in my opinion. A larger patient population asking that same question with a stratification would likely help us to answer this specific question.

DR. VASAN: Thank you.

Dr. Lieu?

DR. LIEU: This is Chris Lieu. I totally agree with what Dr. Nooka said. When we think about enrolling to a U.S. population, we're trying to account for any biological differences that we see, obviously, in our own population. We even see some differences in cell of origin, and then, obviously, the practice patterns. And I think that that's really what's driving the overall survival in the non-Asian regions, is really this idea of what's being given after this therapy, and I think

that that's really driving the overall survival benefit.

So, when you look at the Asian region, I think that the overall survival differences are dramatic, really just truly proven in that group; and then when you look at the non-Asian region, I think it's just unknown.

So the question is, well, can you prove its efficacy using a subgroup analysis? I think we have to be very, very careful, to Dr. Nooka's point, because we can't make any firm conclusions. So then the question becomes, well, are the results generalizable?

I think when you deal with this much of a discrepancy in overall survival benefit, you're certainly not proving that it works in a North American population. And here it's really questionable as to whether there's even a trend towards either no difference or even harm. And we've heard a lot of hypotheses about why we're seeing this difference, but I think it boils down to one thing. We don't know.

So the solution is, obviously, to run this study in a United States population. I'm not saying that lightly. You're talking about five years of drug development and hundreds of millions of dollars. But the simple fact is, if you were designing a study based off of this preliminary data, I think you would have significant concerns about developing a randomized, phase 3 study in the United States with the hazard ratios that we're seeing, and that's why I don't think that it's generalizable.

DR. VASAN: Dr. Spratt?

DR. SPRATT: Dan Spratt, UH Seidman, Case Western Reserve. If they could actually pull up slide 60 from the FDA while I make this point. It's the interaction slide. I think it was table 6 in the briefing document, slide 60. Thank you.

Subgroup analyses, as we've heard many times, are very problematic. Probably the most cited paper that discusses credibility of subgroup analysis from randomized trials was in 2012. I think it's Sun, et al, and there's 11 criteria they

put forth.

This regional difference, 9 of the 11 credibility criteria are met as a credible subset analysis or subgroup analysis. And if you look at these interaction p-values, this is telling you -- when people say that these are underpowered, if you look at PFS, for example, that p-value means there's a 6 in 10,000 probability that this is chance alone that you're seeing differential effects. I don't think there was enough presented today for me to believe that this is just chance alone. I think this is real. I think that more data would be needed to convince me that this is something that is just from the reason Genentech put forth.

I'll bring up, just for context -- and I realize these are other drugs. But just looking through while I've been listening to the presentations, sintilimab in non-small cell lung cancer was just in China. ODAC voted 14 to 1 against approval; tivozanib in renal cell, 13 versus 1 against approval, and less than 10

percent in the U.S. with regional variation; and then Genentech's own product, polatuzumab, which 25 percent in the U.S., it actually was in favor, but it was still controversial, 9 versus 5 of ODAC to vote for approval. But all the hazard ratios were directionally in favor, consistent across the region, which this is completely the opposite.

So I guess, to me, I would really want to see more evidence. It's unfortunate what happened during COVID. I'm sure that played a large role here, but this interaction effect to me is very strong.

DR. VASAN: Dr. Madan?

DR. MADAN: Ravi Madan, National Cancer Institute. I think when we look at therapeutic development, we can't look at it in a vacuum of other therapies available to patients in a region or a country. So I think that has clearly played a role in some of this data being different across the regions. And it's part of the process, it's part of the landscape, and I think it's hard to dismiss it out of hand.

DR. VASAN: Thank you.

Dr. Majkowski?

MR. MAJKOWSKI: Thank you. Paul Majkowski. I'm the patient representative, so I'll try and speak from that perspective, recognizing that I tried to follow the statistics, et cetera. I did the best I could with that.

A couple of things that stood out to me, you have 40 percent of patients who are looking for a cure when you have a refractory or relapsed lymphoma and are ineligible for a transplant. My own experience was I responded to treatment way back when, and I was not in that circumstance, but in my travels in the lymphoma community, I've encountered people who tell the story about needing to go from this, to this, to this.

One of the things that stood out to me in the briefing document is there's no agreed standard of care, so I don't think that -- I remember being on one of these panels in the past, where if we were talking about replacing a treatment as opposed to here, where we're just potentially adding a

treatment, then -- I've strayed a little bit.

I know that the question is, is this generalizable? But I want to give the context of how I approach this issue from the patient perspective. Then we heard commentary, including from one of the public speakers and throughout the discussion, about access, and that's very important. So I look from the context of those sorts of considerations and not disregarding the science. And I'm trying not to speak with my heart instead of my head, but from the patient's chair, I think we need to do that a little bit.

It's difficult to overlook the increased improvement in overall survival. The primary endpoint was met. And as we sat here and spoke about the statistics, again, I'm not a scientist or statistician by trade, but I could not necessarily find a reason why the endpoint was unreliable. And yet, we heard a couple things about the U.S. group being difficult to enroll, the U.S. group having primary refractory disease. That cohort was probably worse off to begin with, so was the

outcome really that unusual or that unexpected?

So answering the question, is this generalizable to the U.S. population, I think from the patient perspective, from the considerations and the context that I would look at, I think that it would be generalizable and could be applicable to the U.S. patient population. Thank you.

DR. VASAN: Thank you.

I would like to ask Dr. McKean if you may have some comments from the community perspective regarding this question, especially as we're talking about generalizability, which I think is very much a question involving all of our patient populations.

DR. McKEAN: Yes. Heidi McKean, Avera Cancer Institute, Sioux Falls, South Dakota. I've been thinking a lot about this accessibility. We all focus on the 25 patients that were enrolled in North America, 11 sites activated but 50-plus approached with this study, and several declined. So that still bothers me about what were the reasons for decline, and I don't believe that it's

all just COVID related.

But just to give a perspective out there for you all, where I live, I come from a state of 400,000 people, and there's one hub that does CAR T transplant. And quite frankly, even with glofitamab, if there's a 40 percent CRS risk, they'd still have to come to our main hub to get that treatment. We just don't simply have enough oncologists and hematologists out there in the community to give this in the smaller cancer setting. So we as a community oncologist need to make sure that this is safe and really effective, and 25 patients is really tough to make that call.

DR. VASAN: Alright. Thank you.

Dr. Frenkl?

DR. FRENKL: Thank you. Tara Frenkl, industry representative from Bayer. Also, I think building on what our patient representative, Mr. Majkowksi, was saying, I think it's hard to ignore the overall positive effect that we see here for which the trial was designed to show. Also, I'm looking for a reason for the difference other

than NALT, and I'm not seeing anything. There's no difference in the PK, and also they mentioned, just on experience with the drug, that there's no regional differences, and the other indications that are already approved.

I can't also pin down a reason why it wouldn't be applicable to the U.S. I do think it's unfortunate with COVID, and also the patient population in terms of them being very refractory; 12 out of 15 patients were refractory in the U.S. group. But we should try to also elevate. The study was not designed to look at these subgroups, especially the small subgroups, 25 patients. So to just pull back up and look at the overall benefit of the study, I think it's hard to ignore.

DR. VASAN: Dr. Spratt?

DR. SPRATT: Dan Spratt, UH Seidman, Case Western. My understanding is this was prespecified to look by region and race, although the definitions were changed. In contrast to what Dr. Fuchs had said, these were prespecified, albeit were not obviously powered for it. That goes back

to the statistical analysis of an interaction effect that there is a significant difference in the differential benefit of this therapy by the subgroups that were prespecified.

So, it's not simply that all of this is just post hoc subset of subset analysis. There's actually a differential in treatment effect. So even if we pretended there is a benefit in the non-Asian population, it's a significantly smaller benefit, even if you believe there is a benefit there, at least from this trial that's in front of us. And whether that's of clinical benefit, that's for everyone, not myself, to decide if that's clinical benefit or not.

DR. VASAN: Dr. Conaway?

DR. CONAWAY: Mark Conaway, University of Virginia. I think if you ask me this question without the first clause, discuss the differential results, if you told me there were 25 participants in the U.S. and asked me are these results generalizable, I think I'd be forced to say I don't know. And when you add in the part about the

differential results, I have even less confidence about the generalizability.

DR. VASAN: Alright. Thank you.

To summarize, we've heard that this trial has met its primary endpoint, yes. Obviously, they're small numbers, hard to extrapolate some differences. One possible mechanism of these small numbers was due to lower enrollment due to COVID. We heard from the patient perspective that there is thought that this could be generalizable.

On the other hand, we've heard, I think, two sets of thoughts. One set of thought is just we don't know. We don't know if this is generalizable, and I think another set of thoughts is saying, no, this is not generalizable based on interaction tests, based on some of the other statistical analyses. Overall though, I think that there's still this question about regional generalizability here.

There was also a comment from Dr. McKean about even the benefit of some of these new therapies like glofitamab may also be outweighed by

the fact that the toxicities could, in the real world, have challenges that we can't foresee from these types of data.

Alright. If there are no further questions, we will proceed.

We will now proceed to question 2, which is a voting question. We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

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

voted as you did, if you want to. We will continue in the same manner until all questions have been answered or discussed.

Question 2, this is a voting question. Are the STARGLO population and trial results applicable to the proposed U.S. patient population?

Are there any issues or questions about the wording?

(No response.)

DR. VASAN: If there are no further questions or comments concerning the wording of this question, we will now begin the voting process.

I'm sorry. Dr. Spratt?

DR. SPRATT: Dr. Spratt. Just to clarify, the STARGLO population and trial results, the overall STARGLO population trial results, are they applicable to the U.S. patient population?

DR. VASAN: FDA, please comment.

DR. SPRATT: I got a nod.

DR. GORMLEY: This is Nicole Gormley, FDA. Yes.

DR. SPRATT: Okay. I am satisfied. Thank you.

DR. VASAN: If there are no further questions, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. SEO: Just a few more moments, everyone. This is Jessica. We're still compiling the results. Thank you.

(Pause.)

DR. SEO: This is Jessica, DFO.

Dr. Choueiri, if you are able to hear me, we're just waiting for your vote to be cast, if you could submit that via e-mail. Please let us know if you have any questions. Thank you.

DR. CHOUEIRI: I will do that. I didn't see the button.

(Pause.)

DR. SEO: This is Jessica again. Just an update, we have received Dr. Choueiri's vote. Just compiling them, and they should be up momentarily. Thank you for your patience.

(Pause.)

DR. SEO: This is Jessica again. The results for question 2 are as follows: 1 yes, 8 nos, and 0 abstentions.

Dr. Vasan?

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

Dr. Choueiri?

DR. CHOUEIRI: Thank you. I'm putting my camera on here. This was a very tough and close call for me. I could buy the NALT effect on the control arm, R-GemOx, despite the back and forth

between the FDA and Roche. I like and buy the censoring message that Dr. Fuchs highlighted, and I agree with it to assess PFS in this situation. I like also the good CR number that Glofit-GemOx had, and that started tipping me favorably.

Dr. Abramson focused on that.

Yes, this could be just a subgroup analysis leading to heterogeneity in treatment effect that can arise just from chance alone with 25 patients, but I would argue that that also adds to the uncertainty; and I fully, completely agree with my colleague, Dan Spratt, on the interpretation of the subgroup analysis.

I kept, during all this time, looking at the result for OS, PFS, ORR, and CR going in the same direction, all inferior in non-Asian with a hazard ratio more than 1. Can we rule out a therapy that works differently in Asian versus non-Asian with the multiple reasons that everybody mentioned? Can this apply to a trial that only included 25 Americans? I think there are other therapies, by the way, and this drug is available as a single

agent.

My worry that tipped me is that if we approve that regimen, the practitioner may give it in patient that could be transplant eligible because we know very well that sometimes this is not cut and dry. That could redefine in their minds what's transplant eligible, what's not eligible, what is refusal, and what's not refusal.

This was an extremely tough call for me. In summary, this result, in order to answer the question, may not be applicable to the 25 patients enrolled in the United States, and this is why I said no. Thank you.

DR. SPRATT: Dan Spratt. I voted no. We're sitting here at the U.S. FDA, and there were 25 patients on this trial from the United States. I think it's imperative -- just like the company was very much willing, and they sound like they're also willing to do so, and they are doing the United States -- to ensure that in China there was sufficient patients, whether in this trial or further expansion cohorts. I'm very glad to hear

they're actively doing so and willing to do so here in the United States. I think our patients deserve that. Thank you.

DR. VASAN: Neil Vasan. I voted no. I kept coming back to this question of, is this a multiregional clinical trial that adheres to the properties of ICH E17? And I think for the reasons that we've all spoken about today, I didn't believe this to be the case.

I will say that another word that I kept coming back to was the word "sufficient," that sponsors should plan to enroll a sufficient number of U.S. participants, and I don't think we can define that as a number or as a percent. But certainly if there's a low percentage of patients enrolled in the trial, and we see this directionality in multiple endpoints, we have to call into question, and we can't know if this therapy may be effective in this specific population. Thank you.

MR. MAJKOWSKI: Paul Majkowski. I voted yes. As I spoke about trying to address this from

the patient perspective, I found it difficult to get past looking at meeting the primary endpoint. And while perhaps it's on the sponsor to meet the burden of proof, maybe I was willing to relax that burden of proof a little bit for the considerations of the patient perspective.

DR. CONAWAY: Mark Conaway, University of Virginia. I voted no for the reasons mentioned in the discussion and in agreement with the reasons brought up by the other panel members.

DR. MADAN: Ravi Madan, National Cancer Institute. I voted no. Therapeutic development in oncology is increasingly a global operation, but deliberate decisions need to be made between expediency and applicability to ensure that data, the results, does apply to the U.S. population. Even beyond today's discussion, this issue gets further accentuated when standards of care or practice patterns in the U.S. differ than other places around the world. So that was the rationale for my thoughts on this. Thank you.

DR. McKEAN: Heidi McKean. I voted no due

to the inconsistencies in the results. I think we need to look at subgroup analyses in this case and, quite frankly, more patients in the U.S. need to be looked at to prove efficacy and safety.

DR. LIEU: This is Chris Lieu. I voted no. What is the bar that we're trying to hit for the United States? The FDA set that bar as stating, to support approval, sponsor should enroll a sufficient number of U.S. participants to support a robust assessment of the safety and effectiveness in U.S. patients. So the question is, was this bar met for our United States patients? And in my opinion, the answer is no. Thank you.

DR. NOOKA: Ajay Nooka from Emory. I voted no. While I'm a strong proponent of drug development, strong proponent of access to therapies, what the question that was asked of me is, are the results from the trial applicable to the U.S. general population? And I'm not convinced with the data that is provided by the sponsor that it is applicable to the general population of the U.S. Thank you.

DR. FRENKL: I would just say that, again, I think the overall results speak to the efficacy of the drug and that there were some extenuating circumstances. On behalf of industry, I know that we always try to have a diverse study that enrolls for the selected population that the drug will serve in the end and, unfortunately, that wasn't the case here with this small population, specifically in the U.S. But I do think that the EU population is also very applicable, and that the race and region are really the same group in this case, although we didn't talk about it, and that it could have been explained by the NALT, which was unexpected. But I appreciate everyone's diverse opinions and the conversation that we've had here today.

DR. VASAN: Thank you.

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

DR. PAZDUR: I just want to emphasize that we are looking at this, obviously, for increased enrollment in the United States. Unfortunately, if

you take a look at all the oncology trials that come to us, only about 20 percent of the population is derived from the United States. We'd like to see robust increased enrollment in the United States. We'd like to understand the reasons why sites are not enrolling in the United States. Potentially, that could be lack of interest because many times the control arms are not appropriate for a U.S. population.

I'd like to make sure that people understand this is going to be an area that the Oncology Center of Excellence is looking at quite closely to ensure that control arms are basically applicable to the United States and represent really current standards here in the United States, not just the weakest control arm that we have. That's not referable so much to this study, but I just wanted to tell you where we're going and our thinking to really try to bolster the enrollment here in the United States. People are developing drugs for marketing in the United States, so it should address our interest here in the United States, and

I just want to make sure that this is clearly delineated here.

Adjournment

DR. VASAN: Great.

Thank you to everyone for this discussion. Thank you to Genentech, to the FDA, to our patient presenters at the public hearing. We will now adjourn the morning session and break for lunch. We will reconvene at 1 pm Eastern Standard Time.

Panel members, please remember that there should be no chatting or discussion of the meeting topics during the break amongst yourselves or with any member of the audience. Additionally, you should plan to reconvene at around 12:50 to ensure you are seated before we reconvene at 1 p.m. Thank you.

(Whereupon, at 11:47 a.m., the morning session was adjourned.)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Afternoon Session

Tuesday, May 20, 2025

1:00 p.m. to 4:56 p.m.

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P R O C E E D I N G S

(1:00 p.m.)

Call to Order

Introduction of Committee

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

My name is Dr. Neil Vasan, and I will be chairing this meeting. I now call the afternoon session of day 1 of the May 20-21, 2025 meeting of the Oncologic Drugs Advisory Committee to order. We'll start by going around the table and introducing ourselves by stating our names and affiliations. We'll start with the FDA to my left and go around the table.

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

FDA.

DR. RICHARDSON: Nicholas Richardson, Deputy Director, Division of Hematologic Malignancies II, FDA.

DR. GORMLEY: Nicole Gormley, Division Director, Division of Heme Malignancies II, FDA. Thank you.

DR. KANAPURU: Bindu Kanapuru, Associate Director for Therapeutic Review, Division of Heme Malignancies II, FDA.

DR. AGGARWAL: Payal Aggarwal, Clinical Reviewer, Division of Hematologics, FDA.

DR. SEO: This is Jessica speaking.

Dr. Choueiri, who is joining us virtually, is momentarily delayed, and we'll introduce him into the record at a later point. Thank you.

DR. SPRATT: Dan Spratt, the Chair of Radiation Oncology, UH Seidman Cancer Center, Case Western Reserve University.

DR. SEO: Jessica Seo, Designated Federal Officer, FDA.

DR. VASAN: Neil Vasan, breast oncologist,

NYU Langone.

MS. POWELL: Joan Powell, myelodysplastic syndrome patient and advocate.

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

DR. MADAN: Ravi Madan, Medical Oncology, National Cancer Institute.

DR. McKEAN: Heidi McKean, Community Medical Oncology, Avera Cancer Institute, Sioux Falls, South Dakota.

DR. LIEU: Chris Lieu, GI medical oncology, University of Colorado.

DR. FRENKL: Tara Frenkl, Head of Global Medical and Evidence at Bayer Pharmaceuticals.

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

the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask 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 topics during breaks or lunch. Thank you.

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

Conflict of Interest Statement

DR. SEO: Thank you, Dr. Vasan.

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

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

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those 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 their 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 discussion of supplemental biologics license application, or sBLA, 761145/S-029, for daratumumab and hyaluronidase injection, or trade name DARZALEX FASPRO, for subcutaneous use, submitted by Janssen Biotech, Incorporated. The proposed indication or use is as monotherapy for the treatment of adult

patients with high-risk smoldering multiple myeloma. This is a particular matters meeting during which specific matters related to Janssen Biotech's sBLA 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. Tara Frenkl is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Frenkl's role at this meeting is to represent industry in general and not any particular company. Dr. Frenkl is employed by Bayer Pharmaceuticals.

We would like to remind members and

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

Thank you, and I'll return the floor to you, Dr. Vasan.

DR. VASAN: We will now proceed with FDA opening remarks, starting with Dr. Bindu Kanapuru.

FDA Opening Remarks - Bindu Kanapuru

DR. KANAPURU: Good afternoon. I'm Bindu Kanapuru, a hematologist/oncologist and the Associate Director for Therapeutic Review in the Division of Hematologic Malignancies II at the FDA. This application is being brought to the committee as it is the first application to be reviewed for a smoldering multiple myeloma indication, a precursor

condition. There are issues as it relates to the endpoints and the results presented by the AQUILA trial that warrant further discussion, as this will have an impact on future development in this space.

The applicant is seeking approval for daratumumab hyaluronidase, henceforth referred to as Dara Sub-Q, a CD38 monoclonal antibody, as monotherapy for the treatment of adult patients with high-risk smoldering multiple myeloma. Dara Sub-Q is planned to be administered for a maximum of 3 years or until progression. The regimen is shown on the slide. Dara Sub-Q is currently approved as monotherapy and in combination for multiple indications for patients with multiple myeloma and newly diagnosed amyloidosis.

The primary evidence for safety and effectiveness for the proposed indication is based on the AQUILA trial. The AQUILA trial is a randomized, phase 3 trial that enrolled patients with a diagnosis of smoldering multiple myeloma who met the protocol-defined criteria for high risk.

Patients were randomized to receive treatment with Dara Sub-Q until progression or a maximum of 39 cycles. The control arm was active monitoring without treatment for 36 months.

The primary endpoint was progression-free survival, defined as time from randomization to progression to multiple myeloma or death, whichever occurred first. The key secondary endpoints were overall response rate, progression-free survival 2, and overall survival. I will highlight some key disease-specific and regulatory considerations relevant to this application.

Smoldering multiple myeloma is a precursor condition. Patients are generally asymptomatic from their disease and have no evidence of organ damage, such as renal failure, anemia, or bone fractures that are commonly associated with multiple myeloma. While patients can progress to multiple myeloma, the rate of progression is variable and depends on the time elapsed since diagnosis, with the greatest risk in the first 5 years. Some patients with smoldering multiple

myeloma may not progress to multiple myeloma even at 10 years.

Several models have been developed to characterize patients' risk of progression to multiple myeloma. Characterizing the risk for development of multiple myeloma allows for appropriate management of patients at high risk of developing multiple myeloma while avoiding overtreatment of those at lower risk.

Before I review the different risk models, I will highlight the changes in the disease definitions which are important to consider.

Prior to 2014, a presence of end-organ damage, defined by the CRAB criteria as shown on the top half of the slide, was required for a diagnosis of multiple myeloma. In 2014, the definitions for both smoldering multiple myeloma and multiple myeloma were updated. Smoldering multiple myeloma patients with specific laboratory or imaging criteria, referred to as SLiM criteria shown on the bottom half of the slide, were identified as having ultra-high risk of progression

and were reclassified as multiple myeloma.

Currently, a diagnosis of multiple myeloma may be based on the presence of either the SLiM criteria or CRAB criteria, and the treatment for multiple myeloma may be initiated prior to the occurrence of end-organ damage.

This slide shows the four frequently cited models for risk classification. The PETHEMA and the MAYO 2008 models on the left, developed prior to the 2014 revisions, assess progression to multiple myeloma based on the CRAB criteria. The MAYO 2018 and IMWG 2020 models to the right assess risk of progression based on the SLiM-CRAB criteria for multiple myeloma. The MAYO 2018 model is recommended by current consensus guidelines for risk assessment.

There is discordance in the criteria used to define the models; however, patients assigned to the high-risk category with the recent models have about 80 to 85 percent risk of progression to multiple myeloma at 5 years.

I will now discuss the treatment landscape

for smoldering multiple myeloma.

Relevant to our discussion today are two phase 3, randomized trials that enrolled patients with high-risk smoldering multiple myeloma, as shown on the slide. Both the trials randomized patients to observation or lenalidomide-based therapies.

While the trials met the protocol-defined primary endpoints, there were notable limitations. In the QuiRedex trial, shown on the left, advanced imaging studies were not required for trial enrollment. Many of the patients included would likely now be reclassified as having active multiple myeloma based on the updated 2014 criteria, so the relevance of this study as it relates to a smoldering multiple myeloma population was questionable.

Additionally, since the trial evaluated lenalidomide and dexamethasone as a combination regimen, the treatment effect of each agent could not be ascertained. The ECOG trial, shown on the right, used advanced imaging for patient selection.

The trial enrolled patients with intermediate and high-risk disease. While the PFS endpoint was met, the benefit was more pronounced in the high-risk group. Notably, there was no benefit in overall survival.

At this time, there are no therapies approved for this patient population. Clinical trials lenalidomide or observation are treatment options. These results highlight the importance of defining the population and the clinical relevance of the endpoints for the smoldering multiple myeloma population.

When considering multiple myeloma, both the disease and treatment landscape has considerably changed. As noted previously, multiple myeloma can be diagnosed and treated prior to the occurrence of end-organ damage based on the SLiM criteria. Additionally, several new therapies and combination regimens have been approved over the last two decades. These include therapies with different mechanisms of action, including the more recently approved CAR T and T-cell directed bispecific

antibodies.

Importantly, CD38 monoclonal antibody-based regimens, including daratumumab-based triplet or quadruplet regimens, are now standard of care in patients with newly diagnosed multiple myeloma. These advances have resulted in significant survival gains, and the median overall survival for patients with newly diagnosed multiple myeloma exceeds 10 years.

With that background, I will highlight the issues identified by the FDA, which are the applicability of the AQUILA results to patients with high-risk smoldering multiple myeloma; appropriateness of the endpoints for high-risk smoldering multiple myeloma population; and the benefit-risk of Dara Sub-Q in patients with high-risk smoldering multiple myeloma.

With regards to the patient population, the ICH E9 guideline for statistical principles for clinical trials notes that the trial subjects must mirror the population intended to use the therapy so that the results can be applicable to patients

in routine practice. Aligning the patient population in the clinical trial with the intended use population ensures that the safety and efficacy results from the trial are applicable to patients who will receive the therapy.

Reviewing the AQUILA trial population, while the trial was initiated in 2017, the protocol-defined, high-risk smoldering multiple myeloma population, shown in the box in gray, did not fully align with any of the available smoldering multiple myeloma risk models; rather, the protocol criteria incorporated components from several models in addition to incorporating other parameters.

Based on the FDA analysis shown in the figure, more than half of the participants on the trial were assessed as intermediate or low risk by any established risk models. Specifically, less than half of the AQUILA trial participants would be at high risk for progression to multiple myeloma based on the current MAYO 2018 model.

These results indicate that a

protocol-defined population may not be representative of patients with high-risk smoldering multiple myeloma as currently defined and raise concerns regarding the applicability of the AQUILA trial results to a population with high-risk smoldering multiple myeloma.

Before discussing the efficacy issues, I would like to highlight some endpoint considerations. Even if a drug's benefit may be supported by scientific evidence from well-designed, properly executed studies, there may be questions about the validity of clinical relevance of one or more endpoints. The ICH E9 guidance states that there should be sufficient evidence that the primary endpoint can provide a valid and reliable measure of some clinically relevant and important treatment benefit in the patient population.

For the secondary endpoints, these could be supportive and contribute to the interpretation of the primary trial results. If the analysis and the results are particularly compelling, secondary

endpoints can provide meaningful information on additional effects of the therapy.

As this is the first therapy proposed for smoldering multiple myeloma, it is important to place the AQUILA endpoints into context of endpoints used to support approvals for cancer, including multiple myeloma.

For multiple myeloma and other cancer approvals, overall survival is an established clinical benefit endpoint. Overall survival is a clinically meaningful objective measure of safety and efficacy and is considered the gold standard for cancer drug approvals. However, in some cancers, overall survival endpoint assessment may require a large sample size that may preclude the use of overall survival as a primary efficacy endpoint. Regardless, overall survival is always evaluated to ensure there is no harm.

PFS can be assessed earlier than overall survival and usually requires a smaller sample size. In patients with active cancer, PFS is considered clinically meaningful depending on the

magnitude of benefit observed, and PFS is thought to or, in some instances, has been shown to correlate with overall survival.

The PFS2 endpoint provides information on delaying second-line therapy in cancers; however, there are limitations that preclude the use of this endpoint for U.S. regulatory purposes for cancer approvals. First, the PFS2 endpoint has not been validated. More importantly, PFS2 may be largely impacted by factors not related to the initial therapy, such as healthcare access, patient discretion, and decisions regarding when to start subsequent therapy and which therapies to administer.

There are no therapies currently approved for smoldering multiple myeloma. An overall survival endpoint may be challenging, as noted previously, and would require even longer follow-up times and larger sample size; however, OS should always be evaluated to rule out harm. Additionally, as overall survival is a clinically meaningful endpoint, its use in trials evaluating

smoldering multiple myeloma warrants further discussion.

With regards to PFS, in smoldering multiple myeloma, delaying progression is primarily delaying a diagnosis of multiple myeloma. The clinical meaningfulness of delaying progression to multiple myeloma on its own, in the absence of significant impact on other endpoints, is uncertain. A PFS2 endpoint may provide an assessment of the impact of treatment that's received in the precursor state on outcomes after development and treatment of multiple myeloma; however, it is subject to the same limitations, with potential confounding due to decisions regarding subsequent therapies.

Reviewing the AQUILA efficacy results, the trial demonstrated statistical significance for the protocol-defined PFS endpoint; that is progression to multiple myeloma or death as assessed by the independent review committee. As a reminder, the 2014 IMWG diagnostic criteria for multiple myeloma is shown in the table.

The reasons for progressive disease on the

AQUILA trial are shown here. The improvement in PFS was primarily seen in the delay in multiple myeloma diagnosis. Of the multiple myeloma events, the majority of the events were based on the lab-based SLiM criteria. There were few CRAB-related, end-organ damage events. While there were events of bone disease, these were noted predominantly on imaging.

As you will hear in the FDA main presentation, not all patients received treatment at multiple myeloma diagnosis, and there was variability in time to initiation of therapy. These results raise uncertainties regarding the clinical meaningfulness of the observed PFS endpoint.

PFS2 was a key secondary endpoint on the AQUILA trial. Despite delaying progression to development of active multiple myeloma in the Dara Sub-Q arm, the time to next progression on the first-line treatment or death was not statistically significantly different between the arms. While the PFS2 results depicted in the KM curve do not

indicate evidence of harm, there are limitations to the interpretation of this data from the AQUILA trial.

Among the patients who had progression, approximately 20 percent did not receive therapy at multiple myeloma diagnosis. Also, about 20 percent received daratumumab-based first-line therapy, which is now the preferred regimen for patients with newly diagnosed multiple myeloma. Given these limitations, the benefit of upfront therapy and the impact of therapy with Dara Sub-Q for smoldering multiple myeloma on outcomes after initial first-line therapy for multiple myeloma in the current treatment landscape is unclear.

Similar to PFS2 results, there is some uncertainty in the overall survival results given the low event rate and wide confidence interval. Again, despite a statistically significant improvement in PFS, the landmark overall survival rates at 5 years indicate a modest difference between the arms. The majority of the deaths occurred following receipt of subsequent therapy,

and the cause of the disease could not be confirmed by the FDA to inform myeloma-specific survival benefit. The overall survival results from the AQUILA trial provide limited information on the benefit-risk assessment, but at this point there is no evidence of harm.

Lastly, I will highlight the safety of Dara Sub-Q in the AQUILA trial. The rates of severity and the type of toxicity should be assessed in the context of the disease condition, which in this case is smoldering multiple myeloma, a precursor condition. There were high rates of treatment-emergent adverse events and high rates of severe and serious adverse events in the Dara Sub-Q arm compared to the active monitoring arm. Common adverse events, including symptomatic events such as fatigue, diarrhea, and musculoskeletal pain, were also higher in the Dara Sub-Q arm.

While PRO assessments can provide valuable information on the patient experience, the PRO results from the AQUILA trial were not informative. The PRO assessments were sparse and the measures

evaluated were not appropriate for this asymptomatic smoldering multiple myeloma population. There are limitations to the PRO data to inform benefit-risk for the proposed patient population.

In summary, the applicant is seeking an indication for the treatment of patients with high-risk smoldering multiple myeloma. This is the first application for a smoldering multiple myeloma population and raises several important issues that warrant discussion.

First, less than half of the participants enrolled in the trial would be considered high risk based on the current criteria. This raises concerns regarding the applicability of the results to a high-risk smoldering multiple myeloma population as currently defined.

Second, while the AQUILA trial demonstrated a delay in progression to multiple myeloma, the majority of the events were asymptomatic. Some patients did not receive therapy or had delayed initiation of therapy despite progression to

multiple myeloma. These observations raise uncertainties regarding the clinical meaningfulness of the PFS results.

Third, there was limited impact in delaying the initiation of second-line therapy for multiple myeloma and on OS. Additionally, only a small percentage received currently approved daratumumab-based triplet or quadruplet regimens. The impact of treatment with Dara Sub-Q for 3 years in the smoldering state on long-term outcomes following treatment with triplet or quadruplet daratumumab-based regimens at multiple myeloma diagnosis is unknown.

Lastly, while the safety profile of Dara Sub-Q is established in multiple myeloma, it is important to consider the proposed patient population who are primarily asymptomatic from the disease. The high rates of severe clinically relevant toxicities in this patient population, including increased rate of infections and fatigue, should be placed in the context of the observed efficacy results. The available data from the

AQUILA trial raise uncertainties regarding the benefit-risk profile of Dara Sub-Q for patients with high-risk smoldering multiple myeloma.

Before I present the discussion topics, I'd like to review the evidentiary criteria for FDA approval. Under the Federal Food, Drug, and Cosmetic Act, for a new approval in the United States, FDA must determine that the drug is safe and effective for use under the conditions prescribed, recommended, or suggested in the product labeling.

The demonstration of effectiveness requires substantial evidence that the drug will have the effect that it's represented to have, and the demonstration of safety requires showing that the benefits of the drug outweighs its risk. The benefit-risk assessment should consider the disease context, which in this instance is a population with a precursor condition for whom observation is an acceptable standard of care.

Taking these points into consideration, we would like the committee to discuss the clinical

meaningfulness of the efficacy endpoints assessed in the AQUILA trial and the benefit-risk of Dara Sub-Q in patients with high-risk smoldering multiple myeloma. Following the discussion, we would like the committee to vote on this question. Do the results from the AQUILA trial provide sufficient evidence to support a favorable benefit-risk profile for Dara Sub-Q for patients with high-risk smoldering multiple myeloma?

This concludes my presentation. Thank you for your attention.

DR. SEO: This is Jessica Seo, DFO. I apologize for the interruption, Dr. Vasan. I just want to take a moment to welcome Dr. Choueiri to the meeting. He's since been able to join.

Dr. Choueiri, could you please unmute and introduce yourself into the record?

DR. CHOUEIRI: Yes. I'm here. Thank you. I joined at 13:07 pm Eastern Standard Time. Thank you.

DR. SEO: Thank you.

I'll return the floor to you, Dr. Vasan.

DR. VASAN: Thank you, Dr. Kanapuru.

Both the 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 participants, including industry's non-employee presenters, to advise the committee of any financial relationships that they may have with industry, such as consulting fees, travel expenses, honoraria, and interest in a sponsor, including equity interests and those based upon the outcome of the meeting.

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

We will now proceed with the presentations from Janssen.

Applicant Presentation - Sen Zhuang

DR. ZHUANG: Good afternoon, Mr. Chair, members of the advisory committee, and members of the FDA. I'm Sen Zhuang, Vice President of Oncology Research and Development from Johnson & Johnson. Thank you for the opportunity today to review the data supporting DARZALEX FASPRO, hereafter referred to as daratumumab, for the treatment of patients with high-risk smoldering multi myeloma.

Daratumumab is a monoclonal antibody against CD38 antigen on the surface of multiple myeloma cells. It is the first biologic ever developed for the treatment of patients with multiple myeloma. Since its initial approval in 2015, daratumumab has become a well established standard of care in frontline and in relapsed and refractory multiple myeloma. More than half a million patients around the world have been treated.

Daratumumab has 10 FDA approved indications,

the most of any myeloma therapy. It is recommended for the treatment of patients with multiple myeloma in every treatment guideline, including the NCCN guidelines. Daratumumab has consistently demonstrated compelling efficacy across approved indications. In pivotal studies, daratumumab-containing regimens provide highly significant and consistent benefit in progression-free survival, with the hazard ratio ranging from 0.37 to 0.63.

Daratumumab-containing regimens also improve overall survival in all studies, with several of them achieving statistically significant advantage. Importantly, daratumumab has a well-established safety profile, including in various combinations.

Recognizing the potential benefit of daratumumab in early stage disease, and based on the strong desires from the myeloma community, we set out eight years ago to assess daratumumab in smoldering multiple myeloma, knowing that it would be a challenging but important study. We designed the AQUILA study based on the learnings from prior

studies in this disease and in collaboration with global myeloma experts. Importantly, we sought advice and obtained agreement on key study design elements, including the definition of patient population and the primary endpoint from global health authorities, including the FDA.

The AQUILA study enrollment criteria, endpoints, and use of advanced imaging to rule out baseline active myeloma addressed many of the limitations from prior studies to provide a robust assessment of a finite daratumumab treatment in high-risk smoldering multiple myeloma. Today, we will present data demonstrating that daratumumab monotherapy positively impacts patients with high-risk smoldering multiple myeloma.

High-risk smoldering multiple myeloma is an asymptomatic malignant condition that is expected to progress to active multiple myeloma at an average of approximately 2 to 3 years. Current standard of care is observation for disease progression.

The AQUILA study is a large international,

randomized, phase 3 study comparing daratumumab monotherapy for up to 3 years versus active monitoring. The results of the AQUILA study demonstrates statistically significant and clinically meaningful improvement in progression-free survival, which was defined as time to progression to active multiple myeloma or death of any cause in this study. Furthermore, the data also show early evidence of a positive trend in overall survival, and the clinical benefit is supported by all secondary endpoints in all relevant clinical subgroups.

Of note, health-related quality of life was comparable between daratumumab-treated patients and those in active monitoring. Safety data from the AQUILA study further confirms the well-established safety profile of daratumumab. Most adverse events reported align with the current labeling and were low grade.

In patients with high-risk smoldering multiple myeloma, a finite duration of daratumumab monotherapy of up to 36 months delays progression

to active multiple myeloma, which requires continuous combination therapy with or without stem cell transplantation. It is our hope that this will be the beginning of our journey to intercept active multiple myeloma and mitigate the suffering and loss of life from advanced disease.

Consistent with the study population of AQUILA, the proposed indication is for the treatment of adult patients with high-risk smoldering multiple myeloma. With this information in mind, here are the agenda of the remainder of the presentation today.

Dr. Sagar Lonial from Emory University will discuss the unmet medical need in patients with high-risk smoldering multiple myeloma. Dr. Robin Carson and Dr. Robyn Dennis from Johnson & Johnson will then present the efficacy and safety results supporting the indication, respectively. Finally, Dr. Vincent Rajkumar from the Mayo Clinic in Rochester, Minnesota will conclude the presentation with his clinical perspectives. We also have additional experts here today to take your

questions. No outside experts have been compensated for their time to prepare or participate in today's meeting.

Thank you, and I'll now turn the podium to Dr. Lonial.

Applicant Presentation - Sagar Lonial

DR. LONIAL: Thank you very much.

I'm Sagar Lonial, Professor and Chair in the Department of Hematology and Medical Oncology and Chief Medical Officer for the Winship Cancer Institute of Emory University in Atlanta. I've worked in the myeloma field for more than 25 years and have witnessed the evolution of treatments in this space, which has been nothing short of outstanding. I was also principal investigator for the initial trial that led to the accelerated approval of daratumumab back in 2015.

While we've increased our ability to delay progression and prolong survival of patients with active myeloma, it's important that we now try and identify patients with earlier disease forms who may benefit from treatment before they develop

myeloma and symptomatic complications that ultimately limit their quality, and in some cases, quantity of life.

Smoldering multiple myeloma is an asymptomatic, predominantly malignant disease that is part of the multiple myeloma disease continuum. But while disease may be smoldering, tumor burden continues to increase silently, putting patients at risk for developing complications and ultimately multiple myeloma.

As you can see, smoldering myeloma sits squarely between MGUS, which has a risk of progression of 1 percent per year, and active myeloma, necessitating the need for full anti-myeloma therapy. So, as we begin to think about the smoldering groups specifically, we need to consider ways to distinguish between those at higher risk of progression versus those at lower risk of progression. Our focus today is the high-risk smoldering subset.

The natural history for patients with smoldering myeloma, shown in yellow, can vary

greatly based on their risk of progression. As noted, these patients face a much greater risk for progression to myeloma than patients with MGUS, roughly 1 percent per year in the MGUS group. Those with the highest risk, shown in red, will progress in approximately the first 2 to 3 years. After about 5 years, the annualized risk of progression lessens. So it's this high-risk group in red that we're focusing on today.

But how should we best determine benefit in this patient population? Meaningful benefit is to delay the time to develop myeloma or death. The PFS endpoint used in AQUILA represents time to develop myeloma, and this is different from PFS in every other clinical trial where a 25 percent increase is a sign of progression. This definition of progression is the development of symptomatic myeloma that requires more intensive therapy.

Because of the well-established and accepted features of myeloma, as shown here, these represent active disease. When a patient presents with any of these factors, we consider them to have myeloma.

Our goal is to prevent the development of these symptoms so that we can prevent the need for intensive therapy. Once a patient is diagnosed with myeloma, they need lifelong, multidrug, toxic combination therapy that will impact their quality of life, while at the same time trying to save their life.

Each of these features can cause grave clinical consequence. Having a clonal bone marrow plasma cell greater than 60 percent, for instance, causes cytopenia, infections, and bleeding events shortly down the road. Patients with a free light chain ratio greater than or equal to 100 are at high risk for developing renal failure. And even anemia, if asymptomatic, signals that a patient's bone marrow is overtaken by malignant plasma cells.

These are not inconsequential asymptomatic laboratory values. They represent a life-changing shift for patients that harbor a high risk of developing cancer in a short period of time. That is why a PFS endpoint as used in the AQUILA study, which represents time to develop myeloma, is

clinically relevant, both for patients and their providers.

Several important papers have established markers that are commonly used to determine a patient's risk for more rapidly developing active myeloma, as shown here. In clinical practice, there's some flexibility about how high risk is defined, as all definitions have been found to lead to similar outcomes.

Other more recent publications have further refined the criteria, with the AQUILA trial enrollment starting in 2017, nicely fitting within the spectrum of this evolution. And I will note that the PFS curve you're going to see for the control arm is consistent with a high-risk smoldering myeloma group, no matter what definition you use on the graph here.

This point is important, as all of these definitions rely on a key set of biomarkers, and patients with elevated level of these disease markers are more likely to progress to myeloma. So while they may differ on the surface, ultimately

they agree and give you the same endpoint.

As you can see across the bottom row, the 2-year risk of progression in high-risk patients is similar regardless of the criteria and aligns with our understanding of the natural history of high-risk smoldering myeloma. We'd also imagine that over time, that these definitions will continue to evolve to further refine these patients at highest unmet need for early intervention, and we'll continue to use updated treatment guidelines to guide our decision making in consultation with our patients.

These are the current NCCN guidelines for management of patients with smoldering myeloma. There are no approved products for this asymptomatic stage of disease. You'll see in the low-risk category that the recommendation is observation for every 3 to 6 months or potentially enrollment in a clinical trial.

These are not the patients we are discussing today. When you look at the high-risk category, you can see that the preferred recommendation is a

clinical trial followed by observation. Lenalidomide is an option; however, it remains a Category 2B recommendation and is only used in fewer than 10 percent of most cases. Most importantly, patients in the community with high-risk smoldering myeloma end up being observed until they develop organ damage such as a fracture or kidney failure, which can impact quality and quantity of life.

To try and address this concern, there have been a number of clinical trials evaluating early intervention to delay disease progression. More than 20 completed or ongoing trials have been conducted in this space, acknowledging this important unmet medical need faced by our patients and our community's desire to fill and address that important need.

The first modern trial was the QuiRedex trial. The second was the ECOG trial. These are low intensity prevention approaches using either lenalidomide or len-dex. Neither were designed or intended as a regulatory registrational study.

Although these studies demonstrated improved outcomes for patients, notable study limitations, including no advanced imaging to exclude active myeloma at baseline and the toxicity of lenalidomide, have prevented the adoption of these treatments as standard of care.

While these trials help to lay the foundation of the need to treat patients with high-risk smoldering myeloma, they are distinctly different from the AQUILA study.

In summary, patients with high-risk smoldering myeloma are likely to progress to multiple myeloma within 2 to 3 years of their original diagnosis, and this was demonstrated in the control arm of the AQUILA study. These are highly functional patients often with a very good quality of life.

Preventing the development of life-threatening myeloma and the need for intensive therapy is very important, but there is no current standard of care for these patients. Patients with high-risk smoldering myeloma seek the ability to

preemptively delay disease progression and prolong their current quality of life.

We need an approved option other than watching and waiting, since for many of these patients, it's not if their disease will progress, but when; and they feel like they're sitting on a ticking time bomb waiting for a complication.

Case in point, in the ECOG trial that I was lead investigator for, we had a patient randomized to observation who presented part way through the trial with new onset bone pain and no change in their biochemical markers. He turned out to have diffuse bone disease at several sites as measured by PET-CT. In clinical practice, we could help such a patient if we had an approved agent for prevention.

It's for all these reasons that I find the results of the AQUILA trial extremely compelling, and I'm really excited and hopeful that we'll be able to have an FDA-approved option to support these patients with the highest risk of progression and end the development of morbidity.

Thank you again. I'll turn the presentation over to Dr. Carson to review the specific results of the study.

Applicant Presentation - Robin Carson

DR. CARSON: Thank you, Dr. Lonial.

I'm Robin Carson, Vice President and Clinical Leader of Oncology Research at Johnson & Johnson. In today's presentation, I'll share the clinical efficacy data for daratumumab that demonstrates statistically significant and clinically meaningful improvement in PFS and indicates improvement in OS. Efficacy is also supported by improvement in all secondary endpoints, and quality of life was maintained compared to active monitoring in patients at high risk for developing multiple myeloma.

Let's first start with the study design for AQUILA. AQUILA is the largest randomized, open-label, phase 3 study of a well-defined, high-risk smoldering population. 390 patients were randomized 1 to 1 to either daratumumab monotherapy or active monitoring.

Patients assigned to the experimental group received daratumumab using the same dosing recommendation in current labeling for active myeloma but stopped after 36 months or confirmed disease progression, whichever occurred first. Patients assigned to active monitoring did not receive disease-specific treatment but underwent the same rigorous monitoring and disease evaluations as the daratumumab group; that monitoring, shown here, included lab evaluation every 12 weeks; yearly central review of imaging, including CT, PET-CT, and MRI; and bone marrow assessment at least every 2 years.

Patients enrolled in the AQUILA study needed to have confirmed smoldering myeloma diagnosed within the last 5 years; they were 18 years and older and had an ECOG performance status of 0 or 1; and they must not have had evidence of active myeloma, including lytic bone lesions. This was confirmed by CT or PET-CT and MRI imaging during screening to exclude bone disease.

Additionally, patients had to have high-risk

smoldering myeloma at study entry. Here are the specific criteria that define high-risk smoldering myeloma in the AQUILA trial. Patients needed to have at least one elevated marker of increased risk. These thresholds were consistent with Rajkumar's 2015 consensus paper that Dr. Lonial showed earlier and were the available criteria when AQUILA enrollment started in 2017.

Turning to the endpoint selection, the primary endpoint was progression-free survival by the accepted International Myeloma Working Group criteria. In this study, PFS was defined as progression to active myeloma as assessed by the independent review committee per SLiM-CRAB criteria, which are shown in the table, or death due to any cause, whichever occurred first. For the diagnosis of progression to active myeloma, patients were required to have at least one of the SLiM-CRAB criteria.

The study also included the key secondary endpoints shown here, with the first three -- overall response, progression-free

survival 2, and overall survival -- controlled for type 1 error.

Now, moving to the demographics of the study, baseline demographics were balanced between groups. The median age of patients was about 64 years, and just over half were female and were mostly white with an ECOG performance status of 0. Disease characteristics were balanced at baseline and representative of patients with high-risk smoldering myeloma.

The median time from diagnosis to randomization was less than one year and 77 percent of patients were randomized within 2 years of diagnosis. Approximately 19 percent of patients had three or more risk factors for progression, and most patients had at least two risk factors.

Now turning to the study disposition, 390 patients were randomized, 194 to the daratumumab arm and 196 to the active monitoring. Of those, one patient in the daratumumab arm did not receive treatment. Sixty-five percent of patients on the daratumumab arm completed all

39 cycles, or 36 months, of treatment compared to only 41 percent of those on the active monitoring arm. The most common reason for early discontinuation in both arms was progressive disease.

Now moving to the results, AQUILA met its primary endpoint of progression-free survival. At a median follow-up of 65.2 months, treatment with daratumumab resulted in a clinically meaningful and statistically significant improvement in PFS, with a 51 percent reduction in the risk of disease progression or death compared with active monitoring, resulting in a hazard ratio of 0.49. Importantly, daratumumab's benefit continued after the 36 months of treatment, which is highlighted in blue, with clear separation from active monitoring.

High concordance was observed across prespecified sensitivity analyses. All analyses strongly favored daratumumab, whether by investigator assessment of progression, computerized algorithm assessment of progression, or across various analyses considering different

censoring rules. All analyses were statistically significant with p-values less than 0.0001, with highly consistent hazard ratios.

Looking at the data by subgroups, PFS benefit was consistently observed across prespecified subgroups. Some smaller groups have wider confidence intervals, but all point estimates favor daratumumab.

Now, let me move to the secondary outcomes, first with overall response. This endpoint was met with 63 percent of daratumumab-treated patients achieving a response. Deep responses were seen with 21 percent of patients achieving a very good partial response and 9 percent achieving a complete response or better.

We also prespecified collection of time to second progression to help assess the impact of treatment on the next line of therapy. We see no detriment in response to frontline treatment for patients who received daratumumab for smoldering myeloma as compared to the patients on the active monitoring arm. PFS2 was longer with daratumumab.

The hazard ratio was 0.58 with a two-sided p-value of 0.032 at the data cutoff. PFS2 assessment is ongoing, as it did not cross the prespecified stopping boundary at this analysis time point.

Now, we will move to overall survival. As expected, there were few deaths during the study of early disease. The overall survival represents a median follow-up of 5.5 years. In total, there were 15 deaths in the daratumumab arm and 26 in the active monitoring arm, resulting in a hazard ratio of 0.52, which indicates improvement in survival with daratumumab treatment. At this time, the results are promising and align with expectations from the PFS benefit.

Looking at additional secondary endpoints of interest, daratumumab delayed the time to first-line treatment of multiple myeloma versus active monitoring with a hazard ratio of 0.46. First-line treatment for multiple myeloma was initiated by 33 percent of patients in the daratumumab group and 54 percent of patients in the active monitoring group.

Patient-reported outcomes were used to understand changes in quality of life and patient report of multiple myeloma-related symptoms over the treatment phase. Since patients reported high quality of life and low symptom burden at baseline, it is critical that there is no decline in health-related quality of life before progression to multiple myeloma.

Patient-reported outcomes were evaluated using questionnaires well established in multiple myeloma and content valid for a high-risk smoldering population. Data from the AQUILA study show that daratumumab monotherapy maintained a patient's health-related quality of life across all outcomes and were comparable to active monitoring.

In summary, daratumumab demonstrated statistically significant and clinically meaningful improvements in the primary endpoint of PFS and across secondary endpoints. Importantly, the study demonstrated favorable early OS trends and comparable quality of life compared to active monitoring.

Thank you very much for your attention. I'll turn the presentation to Dr. Dennis to review the safety data.

Applicant Presentation - Robyn Dennis

DR. DENNIS: Thank you, Dr. Carson.

My name is Robyn Dennis, and I'm a Senior Medical Director of Oncology Research and Development at Johnson & Johnson. I'm pleased to present the safety data reinforcing daratumumab's well-established safety profile in patients with high-risk smoldering multiple myeloma.

As shown earlier in the AQUILA study, 390 patients were enrolled and randomized to either treatment with daratumumab or active monitoring. 193 patients received the daratumumab treatment. Consistent with the AQUILA study design of 36 months or 39 cycles of treatment, the median duration of treatment with daratumumab was 35 months and the median number of treatment cycles was 38.

The daratumumab dosing and predose medication schedule is shown here. Daratumumab

1800 milligrams was administered as a 15 mL subcutaneous injection for up to 36 months or 39 cycles, with more frequent dosing given in cycles 1 through 6. Dosing was then administered once every 4 weeks for the remaining cycles. Predose medications, including an antipyretic, an antihistamine, and a corticosteroid, was recommended 1 to 3 hours prior to each daratumumab administration, and a leukotriene inhibitor was also recommended on cycle 1 day 1.

As expected, there were more adverse events in patients treated with daratumumab compared to active monitoring; however, it is important to note that most adverse events occurred in the first year and were low grade. Grade 3 or 4 AEs and serious AEs were also higher in the daratumumab arm, and 11 patients with reported AEs discontinued daratumumab treatment. Two patients experienced adverse events that led to death in the daratumumab arm, and 4 patients had AEs leading to death in the active monitoring arm.

Shown here are the most common adverse

events that occurred in greater than or equal to 10 percent in either arm. These events align with the current daratumumab label. The most common AEs in the daratumumab arm included fatigue, upper respiratory tract infection, diarrhea, and arthralgia.

Here is the percentage of patients with grade 3 or 4 AEs. The highest incidence of events occurred within the first year. The higher incidence rate in the daratumumab arm is likely due to both the underlying disease process and more frequent dosing of daratumumab as described earlier. Hypertension was the only grade 3 or 4 AE that occurred in greater than or equal to 5 percent of patients, the majority of these events occurring within the first year and in patients who had a history of hypertension.

Here, we show serious adverse events. Pneumonia was the only SAE that was observed in greater than or equal to 2 percent of patients, reported in a total of 4 percent of daratumumab patients, with the highest incidence of these

events occurring in the first year.

Dose modification occurred in 47 percent of patients, and dose or cycle delay was recommended as the primary method for managing treatment-related toxicities. Of note, changes in the actual dose of daratumumab was not permitted per protocol. Thirty-eight percent of patients experienced a cycle delay, and over half of them occurred late in the study during the COVID-19 pandemic. Eighteen percent of patients experienced a dose skipped, and 4 percent of these patients experienced a dose delay within a cycle. Despite this, the mean relative dose intensity was 98 percent.

The most common AES leading to these dose modifications were upper respiratory tract infection, pneumonia, and COVID-19. Most dose modifications were not due to severe or serious adverse events but occurred more frequently with mild AEs due to the asymptomatic nature of these patients. Importantly, there were no differences observed in efficacy for patients with and without

dose modifications.

The rate of any grade adverse events leading to discontinuation of daratumumab was 6 percent, and the grade 3 or 4 adverse events was 3 percent. AEs that were reported by at least two patients that led to treatment discontinuation were fatigue, anxiety, and dyspnea.

Forty-one deaths occurred during the study; 15 were in the daratumumab arm and 26 in active monitoring. The second and third most common reasons of death were disease progression and adverse event, respectively, both more common on the active monitoring arm. Two patients in the daratumumab arm experienced an AE of COVID-19 leading to death. In the active monitoring arm, 4 patients died due to an adverse event. These events were pulmonary edema, cardiac arrest, pulmonary embolism, and cardiac failure.

The cause of death, other, was most common and refers to events that occurred after the AE reporting window or occurred after the start of subsequent therapy. As expected, due to the known

risk of infections with daratumumab, the overall incidence of infections and infestations was higher in the daratumumab arm compared to active monitoring; however, the median duration of any grade infections was 14 days, the same in both arms, and 98 percent of any grade infections in patients treated with daratumumab were recovered or resolved by the time of the data cutoff.

If we look further at AEs of infection over time, you can see a decrease in overall infections or infestations were reported as the study progressed. The most common events by preferred term were upper respiratory tract infection, nasopharyngitis, and pneumonia, all of which occurred less often after the first year of the treatment period.

So, in conclusion, daratumumab was well tolerated in patients with high-risk smoldering multiple myeloma, with clinically manageable side effects consistent with its well-established safety profile. The majority of adverse events were low grade. Mostly occurred within the first year,

resolved quickly, and did not result in treatment discontinuations. And nearly all, 98 percent, of infections resolved with a median duration of 14 days. Importantly, physicians are already familiar in managing the adverse events observed in the AQUILA study, as they were consistent with daratumumab's approved indications.

Thank you for your attention. I'd like to invite Dr. Rajkumar to share his clinical perspective on the data presented.

Applicant Presentation - Vincent Rajkumar

DR. RAJKUMAR: Thank you for your attention. I'm Vincent Rajkumar, Professor of Medicine at the Mayo Clinic. I also chair the International Myeloma Working Group, which developed the diagnostic and response criteria and issues guidelines. It is a pleasure to share my clinical perspective on the data just presented.

As a physician who has led multiple clinical trials and treated patients across the spectrum of multiple myeloma, I've experienced the anxiety that patients have when they are first informed of their

smoldering myeloma diagnosis. They often ask what this means and what the planned treatment course will be. Daratumumab offers us the chance to offer an effective and manageable treatment to our patients, and I am grateful for this long awaited opportunity.

I have had the privilege of working closely for nearly three decades with Dr. Robert Kyle who coined the term "smoldering multiple myeloma." I co-led the paper with him that established the natural history of this disease, showing a 10 percent per year risk of progression to active myeloma, which is tenfold higher than the risk associated with the premalignant MGUS stage.

As the natural history curve indicates, the risk of progression in smoldering myeloma is highest in the first 5 years. Note that 10 percent per year is already an unacceptably high risk of progression, but many risk factors are available that can identify the subset of smoldering myeloma patients with an even higher risk.

The criteria listed here are the ones used

in the AQUILA trial and were based on the consensus paper from 2015. Patients with high-risk smoldering myeloma have a median time to progression to active disease of only 2 to 3 years. This is the group of patients best suited for early intervention to delay end-organ damage, to delay the need for full-blown myeloma therapy, and to improve overall survival.

Observation every 3 to 4 months in high-risk smoldering myeloma appears attractive on the surface, but it risks missing patients prior to progression. The diagnosis is often made only after end-organ damage is detected. I see this in my practice and in the referrals I receive. Patients want options, and we frequently give them false reassurance that we can intervene in a timely manner. In fact, studies show that we are not able to identify 50 percent of progressions in patients with high-risk smoldering myeloma in a timely manner. In the real world, close active monitoring is not feasible, and even if it were, progressions can and do occur between visits.

It is well accepted by myeloma experts that patients with high-risk disease can benefit from early intervention. In fact, we have already moved beyond active monitoring as standard of care in more recent trials of smoldering myeloma, acknowledging the importance of early treatment in high-risk patients.

AQUILA is the last trial with observation as a control arm and likely the last chance for the field to provide patients with an approved choice. This is the essential step one for us to make future advances in myeloma. While the definition of high-risk smoldering myeloma continues to evolve, patients today deserve an effective and safe treatment based on the positive data from the AQUILA trial.

The FDA is asking you to consider several topics, and I'd like to share my clinical perspective on each. First, it's been suggested that the AQUILA population is heterogeneous and includes low and intermediate risk patients by MAYO 2018. Progression-free survival is also being

questioned as an appropriate endpoint, and we are asked to consider the safety profile and any impact of this treatment on patients' quality of life.

The AQUILA trial enrolled a well-defined, high-risk population. Risk stratification in smoldering myeloma is constantly evolving. I have been the lead investigator on almost all commonly used risk stratification models for smoldering myeloma, including the MAYO 2018 criteria and the IMWG 2020 criteria. I can confidently say that AQUILA had a well-characterized, high-risk group of smoldering myeloma, as evidenced by the fact that half the patients in the active monitoring arm progressed to active disease by 3 years. AQUILA also had built in advanced imaging to exclude active myeloma at study enrollment.

It's important to note that patients with smoldering myeloma as defined in AQUILA will all likely progress, some slower, some faster, but all will, or almost all will. Physicians will assess the risk status of patients and use the current risk stratification models and the results of

AQUILA to inform clinical practice. The study population enrolled in AQUILA was indeed a high-risk group, and the study also shows that the criteria can be successfully utilized to identify patients that will most benefit.

The second consideration raised is the study endpoint. Progression-free survival, or PFS, is the primary endpoint that has been used for the approval of most, if not all, myeloma drugs; however, progression-free survival as defined in AQUILA is not the same as progression-free survival defined in myeloma trials. Progression in myeloma trials just requires elevation in biomarkers, serum and urine M protein levels. Progression in AQUILA is far more stringent. It requires patients to meet the current definition of active myeloma. This is a critical consideration.

To appreciate the clinical significance of delaying progression to active myeloma, it's also important to understand that delaying myeloma treatment is life changing. Myeloma treatment essentially means continuous therapy after

diagnosis. It means the start of combination regimens with 3 to 4 drugs. It means maintenance therapy with 1 to 2 drugs until progression and 1 or 2 stem cell transplants in eligible patients. With progression to myeloma comes the reduction in quality of life and higher risk of morbidity and mortality. Delaying the time to active myeloma is in and of itself an extremely important and meaningful endpoint for patients.

In high-risk smoldering myeloma, we can look at three clinically important efficacy endpoints that matter to us and to patients: delaying the time to progression to active myeloma; delaying improving overall survival; and delaying the time when we need to start treatment for active disease.

As this slide shows, the AQUILA trial demonstrates convincing benefit in all three of these endpoints. With the median follow-up of almost 6 years, the AQUILA overall survival hazard ratio shows a 48 percent risk in the reduction of death, an upper bound of the 95 percent confidence interval, which is below 1. This is extremely

meaningful data to patients. The 5-year overall survival difference of 6 percent is not small. Based on prior daratumumab trials, this can potentially translate to an improvement in median survival of 2 years.

Daratumumab has also been studied in many randomized trials for active myeloma. In every randomized trial that daratumumab has been studied, it has shown progression-free survival benefit with longer follow-up, and overall survival benefit has been observed.

Take a look also at the lower panel. At 3 years, only 20 percent of the patients in the daratumumab arm needed to start full active myeloma therapy compared to more than 40 percent in the observation arm. That rate is not reached in the dara arm even at 6 years. It demonstrates that we can prevent or delay the life-altering therapy I mentioned by many years with just limited duration of monotherapy with daratumumab.

Turning your attention to safety, AQUILA shows that treatment with single-agent daratumumab

for 36 months is well tolerated. Daratumumab is not a new drug. Physicians diagnosing smoldering myeloma are already familiar with its safety profile from its widespread use for the last 10 years. Universally, myeloma physicians consider daratumumab to be the safest myeloma treatment we can offer our patients.

The adverse events in the AQUILA trial were mostly mild and transient and occurred early in treatment, mostly within the first year and led to few treatment discontinuations. With daratumumab, we are mainly monitoring patients for infection, and those are usually not severe and are short-lived. Additionally, the preservation of quality of life seen in AQUILA is important, and it's not surprising to me given its well established safety.

For high-risk disease, taking daratumumab monotherapy is very different and safer than multidrug therapies needed when diagnosed with active myeloma. Those therapies have risks that will often lead to hospitalization and will

diminish the quality of life for patients. In my experience, the benefits of daratumumab far outweigh the risks.

To conclude, daratumumab offers patients an early intervention to meaningfully delay their disease progression without negatively impacting quality of life. The adverse events are manageable and well understood, as we have been using daratumumab as a standard of care in myeloma for more than a decade.

Patients with smoldering disease want the ability to choose a proactive intervention besides watch and wait. With informed consent and with shared decision making, these patients can and should be given the option to determine the best treatment path. With early intervention, daratumumab can fundamentally change the multiple myeloma treatment landscape by offering patients with high-risk disease a fixed duration treatment choice with a safe and well-studied drug that delays time to active myeloma, delays the need for full-blown myeloma therapy, and potentially extends

life.

Thank you, and Dr. Carson will return to moderate your questions.

DR. VASAN: Thank you, Johnson & Johnson.

We will now proceed with FDA's presentation, starting with Dr. Payal Aggarwal.

FDA Presentation - Payal Aggarwal

DR. AGGARWAL: Good afternoon. My name is Payal Aggarwal, and I'm a hematologist/oncologist and a clinical reviewer on the Multiple Myeloma Team in the Division of Hematologic Malignancies II at the FDA. Today, I will discuss the FDA's assessment of the daratumumab hyaluronidase application; henceforth, referred to as Dara Sub-Q, proposed for the treatment of patients with high-risk smoldering multiple myeloma. The members of the FDA review team are listed here. My presentation represents their collective input.

The applicant has requested an indication for Dara Sub-Q for the treatment of adult patients with high-risk smoldering multiple myeloma. Dara Sub-Q is proposed for administration as a

single agent until disease progression or a maximum of 3 years. The proposed dosing regimen is shown on this slide. As noted previously, Dara Sub-Q is FDA approved in the newly diagnosed and relapsed or refractory setting for multiple myeloma and in newly diagnosed AL amyloidosis.

My presentation today will focus on the following topics: the applicability of the AQUILA trial results to patients with high-risk smoldering multiple myeloma; the endpoints for high-risk smoldering multiple myeloma; and the safety findings and patient-reported outcomes from the AQUILA trial. Because the disease context and treatment landscape are key to interpreting the results of the AQUILA trial, I will reiterate some key concepts discussed in the FDA introduction.

Smoldering multiple myeloma is a precursor condition with plasma cell proliferation in the bone marrow without end-organ damage. The current definition of smoldering multiple myeloma is shown on the slide. While smoldering multiple myeloma is a precursor condition, there is a risk of

progressing to active multiple myeloma. The risk of progression is variable. Risk of progression is 10 percent per year for the first 5 years with the risk declining after 5 years to 3 percent, and then approximately 1 percent per year after that. The risk also varies based on the presence or absence of specific disease features that will be described in upcoming slides.

Based on the risk model, patients with low-risk smoldering multiple myeloma have a 4 to 10 percent risk of progression at 2 years, while those with intermediate risk have a 26 to 51 percent risk of progression, and patients with high-risk smoldering multiple myeloma have a 47 to 73 percent risk of progression.

With regard to treatment, there is consensus on observing patients with low and intermediate risk. For patients with high risk of progression, observation, lenalidomide, or clinical trials are recommended; however, for all risk categories, observation is an acceptable standard of care. At this time, there are no FDA-approved therapies for

smoldering multiple myeloma despite two phase 3 trials conducted in this patient population.

The first is the QuiRedex trial, which was a phase 3 study that randomized patients with high-risk smoldering multiple myeloma to a combination regimen of lenalidomide plus dexamethasone or observation. The definition of high risk incorporated elements such as percentage of monoclonal plasma cells and immunoparesis. The primary endpoint of the trial was time to progression.

As you can see on the KM curves in the slide, a benefit in time to progression and overall survival was demonstrated with lenalidomide and dexamethasone; however, there were several limitations noted. Regarding the trial population, many of the participants included would likely now be reclassified as having active multiple myeloma based on the 2014 disease definition updates, so the relevance of the study as it relates to a smoldering multiple myeloma population as currently defined was questionable. Additionally, since the

trial evaluated lenalidomide and dexamethasone as a combination regimen, the treatment effect of each agent could not be ascertained.

The second phase 3 trial is the ECOG E3A06 trial that randomized patients to lenalidomide or observation with a PFS primary endpoint. This trial enrolled participants with intermediate and high-risk smoldering multiple myeloma. The primary endpoint was progression-free survival, where progression was defined by the presence of both biochemical disease progression as defined by the IMWG and evidence of end-organ damage by the traditional CRAB criteria for multiple myeloma.

The PFS was longer in the lenalidomide arm, as seen in the KM curve on the left, and statistically significant. Bone progression was the basis for progression in most of the patients in the observation arm followed by anemia. There was no difference noted in overall survival. Key limitations of this trial were that the trial enrolled a heterogeneous patient population of intermediate and high-risk patients. The PFS

endpoint included biochemical progression, and no OS benefit was seen.

Now, I will discuss t he first topic, which is applicability of the AQUILA trial results to patients with high-risk smoldering multiple myeloma.

As noted by the applicant, AQUILA is a phase 3, randomized, open-label, two-arm multicenter trial designed to evaluate the safety and efficacy of Dara Sub-Q versus active monitoring in patients with high-risk smoldering multiple myeloma. 390 patients were randomized 1 to 1 to receive Dara Sub-Q or active monitoring. Dara Sub-Q was administered as a fixed duration for 39 cycles or 3 years, or until disease progression.

Patients in the active monitoring arm were monitored for 3 years without disease-specific treatment. The primary endpoint was PFS defined as time from randomization to progression to multiple myeloma as defined by the IMWG criteria, or death. Essentially, the primary endpoint was the time to development of multiple myeloma or death. The key

secondary endpoints were ORR, PFS2, and OS.

Baseline demographics were overall balance between the two arms. Patients on the AQUILA trial were slightly younger than patients with smoldering multiple myeloma in the United States. The median age of patients enrolled on the trial was 64 years, while the median age of patients with smoldering multiple myeloma in the United States is 67 years.

Additionally, although the trial enrolled 15 percent of the participants from the United States, overall, only 3 percent of the trial participants were Black. The prevalence of multiple myeloma precursor conditions is approximately two-fold higher amongst Blacks than in Whites in the United States.

Before I discuss the AQUILA trial's population, it is important to have a frame of reference for the risk classification models for smoldering multiple myeloma. Four models have been used for assessing risk of progression to multiple myeloma.

The PETHEMA model and the MAYO 2008 model

were developed prior to the 2014 revision to the multiple myeloma definition. The individual components of these models are shown in the figures on the left. In 2018, the MAYO 20/2/20 model was proposed to classify patients at risk for progression. This model is recommended by NCCN guidelines. Lastly, the most recent 2020 IMWG score added features such as high-risk cytogenetics resulting in a new risk score with four risk groups.

As noted in the bottom of the slide, the risk varies from 4 to 25 percent for low risk, to 72 to 85 percent for patients at high risk of progression based on the model used. Identifying patients with the greatest risk of progression allows for appropriate management of these patients while avoiding overtreatment of those at lower risk.

The AQUILA trial protocol definition of high-risk smoldering multiple myeloma can be seen on the right of the slide. Participants were required to have a diagnosis of smoldering multiple

myeloma per IMWG criteria: clonal bone marrow plasma cells of 10 percent and at least one of the high-risk factors listed. While the AQUILA trial was conducted prior to the establishment of the MAYO 2018 model, the criteria used in the protocol did not completely align with any of the available models but instead incorporated criteria from multiple models and additional criteria such as IGA smoldering multiple myeloma and clonal bone marrow plasma cells greater than 50 percent to 60 percent to define patients with high-risk smoldering multiple myeloma.

This slide shows the distribution of protocol-specific criteria amongst both arms. Nearly 75 percent of the participants on both arms met the protocol-defined criteria for serum FLC ratio, and 60 percent met the protocol-defined criteria for immunoparesis.

Retrospective analysis of the trial participants based on the available risk models are shown in the bar graph here. More than half of the trial participants were assessed as intermediate or

low risk by any risk model. The AQUILA trial therefore enrolled a heterogeneous patient population of high, intermediate, and low-risk patients based on the currently used risk models. Based on the consensus MAYO 2018 risk model, less than half of the AQUILA trial participants were categorized as high risk for progression to multiple myeloma; 40 percent of the participants were intermediate risk; and 20 percent low risk.

In summary, the protocol-defined definition of high-risk smoldering multiple myeloma did not completely align with the available high-risk models. The protocol-defined definition of high-risk smoldering multiple myeloma resulted in inclusion of a heterogeneous risk population in the AQUILA trial. Less than half of the trial participants met high-risk criteria using the MAYO 2018 risk model. Because of the heterogeneity in risk of participants in the AQUILA trial, there is uncertainty regarding the applicability of the trial results to patients with high-risk smoldering multiple myeloma.

Next, I will discuss the endpoints for high-risk smoldering multiple myeloma in the AQUILA trial.

As noted in the FDA introductory remarks, for oncology approvals, overall survival is considered a gold standard of endpoints because it is a measure of both safety and efficacy; however, OS may be impacted by subsequent therapy and may require a large sample size to demonstrate treatment effect.

PFS is used as a primary endpoint, as PFS can be assessed earlier than OS and usually requires a smaller sample size. In patients with active cancer, PFS is defined as time to progression or death and is considered clinically meaningful, depending on the magnitude of benefit observed, and PFS is thought to or, in some instances, has been shown to correlate with overall survival.

This figure is a graphical representation of the endpoints as defined in the AQUILA trial. Progression-free survival was defined as the time

from randomization to the diagnosis of multiple myeloma or death. PFS2 was defined as the time from randomization to the date of progression on the first-line treatment for multiple myeloma or death. Overall survival is the length of time from the date of randomization to death. As noted in the FDA introductory remarks, the endpoint considerations for smoldering multiple myeloma, a precursor condition, may be different than those for cancer.

To reiterate, smoldering multiple myeloma is a precursor condition with no therapies currently approved. The clinical meaningfulness of the PFS endpoint as defined in the AQUILA trial and the impact of treatment prior to the development of multiple myeloma and the effect on long-term outcomes is unknown.

In terms of disease progression as defined in the AQUILA trial, there are key definition updates I want to point out. Prior to 2014, the presence of 10 percent or more bone marrow plasma cells, including those who had greater than

60 percent bone marrow plasma cells, three or more grams per deciliter of serum M protein without end-organ damage, defined smoldering multiple myeloma.

In 2014, the diagnostic criteria for multiple myeloma was updated to include biochemical and imaging parameters referred to as SLiM, as shown on the slide. The update resulted in some patients that previously would have been classified as having smoldering multiple myeloma now being classified as having multiple myeloma, particularly in regard to those with 60 percent or more bone marrow plasma cells.

Additionally, people with smoldering multiple myeloma are generally asymptomatic from their disease, and CRAB criteria are absent. In contrast, patients with multiple myeloma may be symptomatic and are diagnosed based on CRAB or SLiM criteria, and a diagnosis of multiple myeloma generally requires treatment, which is usually initiated with triplet or quadruplet regimens.

In the AQUILA trial, the primary endpoint of

PFS was defined as the time from date of randomization to date of progression to multiple myeloma using SLiM-CRAB criteria or death. In other words, progression was defined as the diagnosis of multiple myeloma.

I will now discuss the PFS primary endpoint.

Median PFS was not reached in the Dara Sub-Q arm and was 41.5 months in the active monitoring arm. As the KM curve on the right demonstrates, a statistically significant improvement in PFS was seen in the AQUILA trial. Overall, the results across the different subgroups were consistent with the primary PFS analysis. Based on the MAYO 2018 criteria, the benefit was most pronounced in the high-risk subgroup. The KM curve on the right shows the PFS in the MAYO 2018 high-risk group.

I will now highlight some observations of the PFS results from the AQUILA trial.

As mentioned previously, PFS was the time from randomization to progression, which was a multiple myeloma diagnosis using SLiM-CRAB criteria or death, whichever occurred first. The rate of

death was very low, 3 percent, and equal on both arms; therefore, improvement in PFS was primarily due to delay in diagnosis of multiple myeloma.

The reasons for progressive disease on the AQUILA trial are shown here. About 30 percent of the participants were diagnosed with multiple myeloma based on imaging or lab-based SLiM criteria, while approximately 10 percent were based on end-organ damage related CRAB criteria. The most common reason on both arms was asymptomatic elevation of serum free light chain ratio greater than 100. In summary, the majority of AQUILA participants had a multiple myeloma diagnosis on the basis of SLiM criteria. When evaluating the events due to CRAB criteria, no participant experienced events of renal and organ damage, and less than 1 percent of the participants experienced hypercalcemia.

There were higher rates of progression events due to anemia in the active monitoring arm; however, before progression was declared based on an anemia event without CRAB signs or symptoms,

additional diagnostic tests such as iron, ferritin, transferrin, Coombs testing were recommended by the protocol. The results of these diagnostic tests to evaluate other causes of anemia were not collected by the applicant.

Furthermore, of the 14 participants on the active monitoring arm and 2 patients on the Dara Sub-Q arm who met criteria for anemia, the majority of patients had only minor changes in hemoglobin levels. The bar graph here depicts participants' study entry hemoglobin and documented hemoglobin at progression. The median change in hemoglobin was 1.7 grams per deciliter. Only three participants with an anemia event had a clinician-reported AE of anemia, and it was grade 1. None of the participants with anemia events received transfusions.

In terms of bone disease events for the CRAB criteria, these events were based on lesions detected primarily by imaging. Only three of these participants had bone symptoms such as pain or fracture with bone lesions.

I will now discuss the receipt of therapy in the patients diagnosed with multiple myeloma on the trial. Not all participants initiated therapy for multiple myeloma. About 20 percent of participants diagnosed with multiple myeloma did not receive therapy. The reasons for not receiving therapy are in the table to the right, and in approximately two-thirds of the patients, the reason for not initiating therapy were listed as controlled disease, or no progression in local labs, or imaging.

Among the participants who initiated therapy, the median time from diagnosis of multiple myeloma to therapy initiation was approximately 2 months in the active monitoring arm and 3 months in the Dara Sub-Q arm. For approximately 25 percent of patients, therapy was not initiated until 6 months after diagnosis, and some patients did not initiate multiple myeloma therapy up to 50 months following multiple myeloma diagnosis.

The data presented in the last two slides raise additional concerns regarding the PFS

endpoint as defined and assessed in the AQUILA trial. In general, patients who are currently diagnosed with multiple myeloma would be expected to start therapy soon after a multiple myeloma diagnosis; however, in the AQUILA trial, even after a multiple myeloma diagnosis, investigators chose not to initiate multiple myeloma therapy in about 20 percent of patients. Furthermore, the most common reason investigators did not initiate multiple myeloma therapy was lack of progression.

Even amongst the participants who initiated therapy, there was a wide range of time to initiation of therapy, with some participants not initiating therapy until 4 years after diagnosis. If investigators are choosing to not initiate treatment or delaying initiation of treatment, the clinical meaningfulness of the PFS endpoint as assessed in the AQUILA trial is unclear.

In summary, while the AQUILA trial met the primary endpoint of PFS as defined, it did so primarily by delaying a diagnosis of multiple myeloma. The majority of the events were due to

SLiM criteria as opposed to symptomatic CRAB criteria or death. Additionally, 20 percent of participants did not receive therapy after multiple myeloma diagnosis, and even in those who received therapy, the time to multiple myeloma therapy varied. The clinical meaningfulness of the observed improvement in PFS is unclear.

Next, I will discuss the PFS2 endpoint.

PFS2 has not supported approval of therapies for patients with cancer in the United States, as it can be confounded by factors not related to initial therapy. In precursor conditions, PFS2 may provide an assessment of the impact of treatment received in the precursor state on outcomes after development of multiple myeloma. As depicted in the figure, PFS2 is defined as the time from randomization to the date of progression on the first-line treatment for myeloma or death.

In the AQUILA trial, the PFS2 endpoint was not adequately powered for efficacy. Despite delaying progression to development of active multiple myeloma in the Dara Sub-Q arm, the time to

next progression on the first-line treatment or death was not statistically different between the arms. The median PFS2 was not reached in either arm. In the high-risk group defined by the MAYO 2018 model, there were 15 PFS2 events in the Dara Sub-Q arm and 19 events in the active monitoring arm. The confidence interval crossed 1, and the results were not meaningfully different between the two arms.

While PFS2 may provide an assessment of the impact of treatment reserved in the precursor state on outcomes after development of multiple myeloma, the results can be impacted by receipt and type of therapy received at multiple myeloma diagnosis. As noted previously, among the patients who had progression determined by IRC, 20 percent did not receive therapy at multiple myeloma diagnosis.

Amongst the participants who received multiple myeloma therapy, there was a wide range in the type of therapies administered, including several that are not approved for patients with newly diagnosed multiple myeloma.

Daratumumab-based triplet and quadruplet regimens are the now preferred regimens for patients with newly diagnosed multiple myeloma with demonstrated survival benefit in this setting; however, among those who develop multiple myeloma, only a quarter of the patients on the active monitoring arm and about 15 percent of patients in the Dara Sub-Q arm received daratumumab-based regimens. Given these limitations in the data, the impact of treatment with Dara Sub-Q for smoldering multiple myeloma on subsequent response to anti-CD38 treatment at multiple myeloma diagnosis is unclear.

In summary, despite delaying diagnosis of multiple myeloma, the PFS2 results were not substantially different between the arms. While exploratory, similar results were noted in the MAYO 2018 high-risk subgroup. Many participants of the AQUILA trial did not receive therapy upon progression to multiple myeloma, and if they did, they did not receive regimens considered to be standard of care for patients with newly diagnosed multiple myeloma. The impact of treatment of

high-risk smoldering multiple myeloma on the outcomes after first-line therapy is unclear.

Next, I'll discuss considerations regarding overall survival as an endpoint in smoldering multiple myeloma.

OS was a key secondary endpoint on the AQUILA trial; however, the trial was not adequately powered to show an OS improvement. Additionally, the OS results are immature, as only 41 of the planned 107 OS events have occurred. At 5 years, the difference in OS rates between the two arms was modest at 6 percent. The FDA conducted additional analysis to evaluate the OS results on the AQUILA trial to inform benefit-risk assessment.

FDA explored OS results in the high-risk group defined by the MAYO 2018 model. There were 24 deaths, 10 in the Dara Sub-Q and 14 in the active monitoring arm. The MAYO 2018 KM curve is based on a limited number of OS events; however, it is important to consider, as this subgroup is most reflective of the intended use population.

When considering treatment for a precursor

condition such as smoldering multiple myeloma, it is important to consider the impact on later treatment. Daratumumab-based triplet or quadruplet regimens are the current standard of care for patients with newly diagnosed multiple myeloma, and treatment has shown to prolong overall survival.

It is important to evaluate if treating with single-agent Dara Sub-Q for 3 years, at the stage of smoldering multiple myeloma, will have an impact on the OS effect of daratumumab-based regimens received at multiple myeloma diagnosis; however, as noted previously, in the AQUILA trial, only 20 percent received daratumumab-based regimens upon a diagnosis of multiple myeloma overall.

At this time, the impact of receipt of Dara Sub-Q as monotherapy, for 3 years for smoldering multiple myeloma, on the ability to receive standard of care daratumumab-based triplet or quadruplet regimens, or outcomes after receipt of these regimens for newly diagnosed multiple myeloma, is unclear. The clinical benefit of treatment in the precursor stage versus at the time

of multiple myeloma diagnosis is unclear.

FDA evaluated the cause of deaths to assess impact of the treatment on myeloma-specific survival. When considering all deaths on the AQUILA study, the majority of deaths were categorized as other, with low rates of death events related to progression or adverse events. FDA requested additional information regarding the causes of these deaths. The applicant stated that detailed information was not available because the majority of deaths occurred after receipt of subsequent therapy. Because detailed narratives were not available, FDA could not determine if the deaths were due to progression or other causes to evaluate myeloma-specific survival.

Given the importance of OS as a clinical benefit endpoint, the FDA performed an analysis to estimate the target number of OS events and the required sample size if the trial was powered to demonstrate an OS benefit based on regular methods. Using the assumptions from AQUILA based on 80 percent power and a two-sided type 1 error rate

of 0.05, the required number of OS events would be 686, which would not be feasible.

This does not imply that OS would always be impracticable in this setting. With more effective therapies targeting a smaller hazard ratio, it may be possible to assess OS for efficacy. Regardless, OS should always be assessed for safety.

In summary, the AQUILA trial was not designed to show a significant improvement in OS. The OS results are immature, and at this point, there are fewer events than were initially anticipated. The majority of deaths thus far were not due to progression or adverse events, but rather were categorized as other and occurred following receipt of subsequent therapy. The OS results from the AQUILA trial provide limited information on the benefit-risk assessment, but at this point, there is no evidence of harm.

This slide aims to summarize some of the endpoint issues in smoldering multiple myeloma. The top figure shows the journey of a hypothetical patient diagnosed with smoldering multiple myeloma

who is observed without treatment, while the bottom figure represents the journey for a patient that is diagnosed with smoldering multiple myeloma and receives treatment. If there is only a delay in a diagnosis of multiple myeloma without improvement in PFS2 or OS, the clinical meaningfulness of the observed improvement in PFS is unclear.

Additionally, it is critical to understand the impact of treatment in the smoldering state on the patient's ability to respond to regimens known to provide benefit in patients with newly diagnosed multiple myeloma.

The top figure shows the current treatment paradigm for multiple myeloma. In the current landscape, patients who are diagnosed with multiple myeloma generally initiate triplet or quadruplet daratumumab-based regimens at the time of diagnosis. The bottom figure represents the treatment paradigm based on the AQUILA trial.

Currently there is insufficient data to evaluate the impact of receiving Dara Sub-Q as monotherapy for 3 years for smoldering multiple

myeloma on the ability to receive or benefit from standard of care daratumumab-based triplet or quadruplet regimens at the time of multiple myeloma diagnosis.

Now, I will discuss safety findings and PRO results from the AQUILA trial.

The median duration of treatment in the Dara Sub-Q arm was 35 months. Nearly all participants on the Dara Sub-Q experienced treatment-emergent adverse events. Only 40 percent of the participants on the Dara Sub-Q arm experienced grade 3 or 4 treatment-emergent adverse events compared to 30 percent on the active monitoring arm.

Approximately one-third of the patients in the Dara Sub-Q arm compared to approximately one-fifth of the patients in the active monitoring arm experienced serious adverse events. Approximately half of the patients experienced AEs that required dose modifications and 6 percent had clinically significant adverse events leading to treatment discontinuation.

In the participants enrolled on the AQUILA trial, 17 percent of the participants experienced an infusion-related reaction of which 2 participants developed grade 3 reactions related to Dara Sub-Q administration. The rate of infections was also double on the Dara Sub-Q arm compared to that of the active monitoring arm. Notably, although anemia was cited as a reason for progression and higher in the active monitoring arm, there were no differences in the rates of lab-based anemia events between the arms.

The most common treatment-emergent adverse events are shown in the table. The rates were all higher in the Dara Sub-Q arm. As most of these adverse events are primarily symptomatic events, this could play a role in the quality of life for people who are generally asymptomatic.

Now, I'd like to discuss the patient-reported outcomes for this trial.

PROs were measured using two scales but were collected sparsely during the AQUILA trial. The assessment frequency was baseline week 12, 24, 60,

and yearly; thereafter, until end of treatment or the active monitoring phase. Although patient-reported outcomes can provide valuable data in clinical trials, the FDA considers the PRO results from the AQUILA trial as uninformative.

First, PROs were collected sparsely. Second and most importantly, smoldering multiple myeloma is generally an asymptomatic condition, and multiple myeloma diagnosis in AQUILA was based primarily on biochemical or imaging parameters; therefore, multiple myeloma disease symptom PROs are insufficient to capture changes in symptoms and function for this trial population.

Third, the AQUILA trial and the PRO endpoints were not designed to detect a difference between arms in terms of patient-reported symptoms and functioning. With these limitations, similar PRO scores between treatment arms do not provide evidence of tolerability or equivalence; therefore, FDA cannot make any conclusions based on this PRO data, and we do not agree with the applicant's interpretation of the PRO results.

In summary, the overall adverse event rates were higher in the Dara Sub-Q arm. This included grade 3 to 4 serious and adverse events leading to treatment modifications. Additionally, there were issues with the PRO data that limit the ability to inform the benefit-risk assessment.

Now, I will summarize the FDA's assessment of benefit-risk based on the AQUILA trial results.

For the AQUILA trial, there are many important considerations. The applicant is seeking an indication for Dara Sub-Q for the treatment of adult patients with high-risk smoldering multiple myeloma; however, less than half of the participants enrolled on the trial would be considered high risk based on the current criteria. The AQUILA trial participants may not be reflective of the patient population for whom the drug is intended.

While a PFS improvement was observed in the Dara Sub-Q arm compared to the active monitoring arm, the majority of PFS events were asymptomatic. Additionally, not all patients received therapy at

multiple myeloma diagnosis, and some had delayed initiation of therapy. These findings questioned the clinical meaningfulness of the observed PFS results.

The available evidence also does not demonstrate a meaningful impact on delaying the initiation of second-line multiple myeloma therapy or on OS results that raise additional uncertainty regarding the benefit of the therapy. The participants with high-risk smoldering multiple myeloma received treatment for 3 years. The higher rates of toxicities observed in the Dara Sub-Q arm and the long duration of treatment must be placed in the context of these efficacy results.

Overall, the limitations of the endpoints to inform benefit and the noted safety concerns observed in the smoldering multiple myeloma patient population in the AQUILA trial raise uncertainties regarding the benefit-risk assessment for Dara Sub-Q for patients with high-risk smoldering multiple myeloma.

We would like for the committee to discuss

the clinical meaningfulness of the efficacy endpoints assessed in the AQUILA trial and the benefit-risk of Dara Sub-Q for the intended high-risk smoldering multiple myeloma population in context of the results from the AQUILA trial.

We will ask the committee to vote on the following question. Do the results from the AQUILA trial provide sufficient evidence to support a favorable benefit-risk profile for Dara Sub-Q for patients with high-risk smoldering multiple myeloma? Thank you for your attention.

Clarifying Questions

DR. VASAN: Thank you.

We will now take clarifying questions to the presenters. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That

is all for my questions," so that we can move on to the next panel member.

Are there any clarifying questions for the presenters?

I'll start. This is for the FDA, slide 57.

I just wanted to pressure test this PFS endpoint a little more. It's clear from the data that most PFS events in AQUILA were based on SLiM biochemical progression rather than the symptomatic CRAB events, so I'm wondering if you have been able to separate -- if we call this PFS SLiM and PFS CRAB -- what that PFS actually looks like, deconvoluting this PFS to gain better meaning of what this really means.

DR. KANAPURU: Thank you for that question. If I understand it correctly, you are asking if the FDA looked at the PFS results just based on either CRAB or just based on SLiM criteria?

DR. VASAN: Correct, specifically the CRAB or death.

DR. KANAPURU: Yes. We did look into those results. I can just comment that when you actually

look at the PFS events based on CRAB criteria, based on looking at the slides, the PFS events that are primarily based on CRAB criteria, the number of events were really small. But within that limitation, when we did look at just PFS based on CRAB criteria, the PFS results were consistent with the primary PFS results. The hazard ratio was 0.29, but we acknowledge that the number of events overall were small for the CRAB criteria.

DR. VASAN: Thank you.

Dr. Spratt?

DR. SPRATT: Dan Spratt, UH Seidman, Case Western. For either the applicant or the FDA, if someone did the analysis, I'm curious. In the active monitoring arm, patients who did or did not progress, can you show me the survival curves within that group? What were the overall survival curves in those who did progress and who did not progress by the definition in the trial?

DR. CARSON: Robin Carson, Johnson & Johnson. We did not look at the data how you're asking for it. We just looked at overall survival,

in general, for all patients, whether they progressed or didn't progress; and that's the data that was presented that showed the hazard ratio of 0.52.

DR. SPRATT: Thank you.

Did the FDA look at this to see what the survival differences in people who did or did not progress?

DR. ZHOU: This is Xueping Zhou, statistical reviewer, FDA. Can we pull up backup slide 118?

We actually looked at the PFS2 endpoints based on whether participant has a PD event, meaning whether the participant has been diagnosed with multiple myeloma by the investigator. As shown in this slide, actually, the upper curves denote those without PD per investigator prior to a landmark. Here we used landmark to address the potential guarantee-time bias, but the results should be very similar across different landmarks.

As you can see, for the treatment effects for those without PD per investigator, the curves are overlapping with each other, as well as the

lower two curves signals those with PD per investigator, and the curves are overlapping with each other.

DR. CARSON: If we could just respond also?

DR. VASAN: Yes.

DR. CARSON: Dr. Rajkumar, please.

DR. SPRATT: Thank you. So you don't have the actual survival, the OS curves?

DR. VASAN: Johnson & Johnson?

DR. CARSON: We don't have a response. Thank you.

DR. VASAN: Dr. Lieu?

DR. LIEU: My question is regarding PFS2 and the active treatment monitoring arm, and it's to the applicant and the FDA, depending on whether or not anybody has done this analysis. But one of the concerns with PFS2 is that only 24 percent of the active treatment monitoring arm received a daratumumab-containing regimen for the treatment of multiple myeloma.

My question is in regards to PFS2. And I know that there probably are not enough events to

do this analysis, but do we have an idea of what PFS2 looks like in the active treatment monitoring arm in patients receiving a daratumumab regimen, a regimen considered to be standard of care, compared to the treatment arm?

In all honesty, there may not be enough events in 24 percent of the patients in the active treatment monitoring arm to do an analysis; but, I mean, again, that's one of the concerns that's being raised by the FDA.

DR. CARSON: Yes. My apologies. We haven't performed the data that way because the events are small, but what I can't say for you is, of the patients who received a CD38-containing regimen, and we include isatuximab when we do these analyses, there were 16 patients in the daratumumab arm that went on to receive an anti-CD38-containing regimen. All of those patients are responding to therapy and still on therapy to date, now, on the study that's still ongoing.

DR. LIEU: Thank you.

DR. VASAN: FDA?

DR. KANAPURU: Yes. We did not look at the PFS2, but we did do an analysis of OS, looking at patients who went on to receive dara in the active monitoring arm. I'm going to ask my statistical colleague to respond.

DR. ZHOU: If we can pull up backup slide 125? Actually, here we conducted a sensitivity and supplementary analysis adjusting for any subsequent therapy using both arms, using the IPCW method as well as the two-stage model. We also did naive censoring at the start of any subsequent therapy in both arms, resulting in a point estimate less than 1 but with wide confidence intervals. These results suggest that the OS data is not mature and the primary analysis for OS results may not be robust.

DR. LIEU: Thank you.

DR. VASAN: Dr. Madan?

DR. MADAN: Ravi Madan, National Cancer Institute. If we could pull up sponsor slide number 27? I just want to also say that the FDA and the sponsor gave excellent presentations, which

is why we're all asking such nuanced questions here.

I'm trying to focus in on the question of risk and benefit here. When we first look at this, you're kind of dialed into the 3 years and the separation between the curves, and it's about 20 some odd percent, but 51 percent haven't progressed.

My question is actually closer to the one-year mark here because it looks like, unfortunately, the patients at greatest risk for progression, there doesn't seem to be as much separation in the curves, and that seemed to be true also when the MAYO risk scoring was done by the FDA. My question, I guess, either for the sponsor or the FDA is, let's say at one year, is the separation of the curves at that point statistically significant, or does anybody want to comment on this in general?

DR. CARSON: I can comment in general on what the risk factors were in those patients who had early progression between the two arms of the

study, but not the statistical significance.

DR. MADAN: No, just more the separation on the curves. In other words, are we having an impact in that when we're trying to figure out who's benefiting here, it's clear that there's a subset of patients that are benefiting; but are we benefiting the patients that are progressing at one year with this regimen? Because again, that's when the separation happens.

DR. CARSON: I'd like Dr. Rajkumar to respond to your question, please.

DR. RAJKUMAR: See, smoldering multiple myeloma is a malignancy. It's asymptomatic, but it's a malignancy and may require the two or three drugs like we use for myeloma to actually make a difference in the very first year, quickly. But we cannot get there unless we show something is better than nothing, and there are no more trials with observations. So my problem here is that daratumumab has such a profound effect, but it does take time. And the very first-year patients we may not be able to help, but that's because we're using

one drug.

DR. MADAN: Okay. I think it does raise the question that if we can identify those patients pre -- that would be the target population to really impact. Okay. Thank you, and end of my question.

DR. CARSON: If I could maybe make one more comment to your question, the patients that were progressing very quickly were the patients who had more than or three risk factors. So my interpretation is they're telling us they need more than just dara. But most of the patients are benefiting from just dara alone, and that is the key to this study and the overall results of the study. But that's a finding that we're only able to tell from Duke performing this study.

DR. VASAN: FDA?

DR. ZHOU: Can we pull up backup slide 129? Actually, the late separation of the curve may be partially due to disproportional censoring, especially early censoring between the two arms. As shown in this slide, you can see a lot of the

censoring before one year due to subsequent therapy used, and this may partially mask the treatment effects for dara arm.

DR. CARSON: So, in terms of the early censoring that she's showing here, the main reason for early censoring was actually receiving subsequent therapy with anti-myeloma therapy prior to progressive disease by IRC. That is actually one of the sensitivity analyses that we did perform on the primary analysis of PFS. That's shown in the core slide deck 28, and those results are highly consistent, whether we censor or don't censor those patients who went on to receive subsequent therapy without progression in the study. That's the middle row on this with a ratio of 0.48, so highly consistent with the primary results of the study.

DR. VASAN: Dr. Frenkl?

DR. FRENKL: Tara Frenkl, industry representative from Bayer. I have a couple questions. Maybe I'll start either with Dr. Aggarwal of Kanapuru.

Personally, I'm wrangling a little bit with the questioning of the clinical meaningfulness or the significance of progression to PFS. Whether it's SLiM or CRAB, they're both set by the biggest experts in the world on this with the IMWG, and then it was also determined by an independent review committee.

So, are you saying there should be different criteria that are set for the progression of clinically meaningful multiple myeloma?

DR. AGGARWAL: So, thank you for your question, Dr. Frenkl. We acknowledge that the diagnosis of multiple myeloma includes both SLiM criteria and CRAB criteria. In the AQUILA trial, the progression events were either SLiM-CRAB criteria, but they were based on lab changes or imaging only.

So like I mentioned, for the people that had progression events for bone events, only three of these people were actually symptomatic in terms of fractures. And additionally, despite having progression, 20 percent of patients did not receive

the first-line multiple myeloma therapy; and then, for those who did receive therapy, there was a wide range in the time to initiation of therapy. In the active monitoring arm, the median time to therapy initiation was approximately 2 months, and then 3 months in the Dara Sub-Q arm.

So the the question really is, if these patients are progressing and investigators are choosing not to initiate multiple myeloma therapy at that point, it questions the clinical meaningfulness of the PFS events. And this is a therapy that patients would get for 3 years, potentially, and it does have treatment side effects. So taking all of that into consideration, that's really where we were coming from with the clinical meaningfulness of the PFS endpoint.

DR. FRENKL: Thanks. I do understand the association with the clinical symptoms. But also, again, if the experts have said that it's just the lab criteria, that's kind of good enough for me; I don't know about anyone else. And we're also trying to prevent the progression. We don't want

them to have symptoms or end-organ damage eventually. So, thanks.

DR. GORMLEY: This is Nicole Gormley. I'd like to comment as well.

DR. FRENKL: Yes?

DR. GORMLEY: I think part of the issue is we're really in unchartered territories here when we're thinking about initial treatment for a precursor condition. And just to be frank, I think the thought initially with intervening in a precursor disease is that you would have more of an impact on long-term outcomes, such as overall survival in particular.

I think the thought of intervening early is that hopefully you can possibly lead to curing some of these patients. And here, I think there there are questions about what is the clinical meaningfulness of delaying diagnosis without necessarily having large impacts on later long-term clinical outcomes; so that's theoretically or conceptually.

I think, additionally, the results from this

trial raise questions regarding the clinical meaningfulness of the PFS endpoint as it was assessed in AQUILA given the items that Dr. Aggarwal mentioned in terms of a significant number of patients not receiving treatment, actually, when they were diagnosed or having delays in the treatment.

So, with all due respect to the thought leaders in this field, this is an important regulatory consideration in terms of what is the clinical meaningfulness of the progression-free survival endpoint and the progression-free survival results that were observed in this trial and in light of the questions regarding long-term outcomes. Thanks.

DR. CARSON: Dr. Vasan, if I could respond?

DR. VASAN: Yes, please.

DR. CARSON: There were several things brought up here, so I want to try to approach them one by one.

One of the points made was the median time to starting subsequent therapy was in this study.

I think it's important to note that to have progressive disease by biomarkers, you have to confirm it. So it's not just one assessment. They have to have two consecutive assessments to confirm that progression. So the time from one time point to the next that's protocol specified is every 12 weeks, and the date of the progression is the first sign of that progression.

So even though they confirm that progression 12 weeks later, the timing of the progression is with that first assessment. So that's why they're not starting subsequent therapy until after they confirm, and that could be anywhere from the time of the initial progression to they can bring the patient back sooner to confirm it, or the patient may not come back until the 12-week mark that the protocol specifies.

So that's the difference in the timing of the initiation of therapy. A lot of that is driven by when the disease progression is confirmed, so that's one point of clarification.

Then, in terms of overall survival, patients

in the study are expected to have overall survivals longer than 10 years with frontline myeloma therapy that continues to improve, and continuing to improve since the study started in 2017 when dara wasn't even a frontline available regimen. So over the course of the study, where dara moved into the frontline, overall survivals continued to improve. The study was originally designed to only show a trend in overall benefit in survival, so only to have a hazard ratio of 0.8.

So I just want to clarify those points, and then Dr. Lonial wanted to comment further about the clinical meaningfulness of the primary endpoint.

DR. LONIAL: Thank you. Sagar Lonial from Emory University in Atlanta. I want to go back just a little bit because in a disease like myeloma, we are always biomarker driven. Other than prostate cancer, we are the only cancer that uses biomarkers to drive disease status and disease progression, so biomarkers are important.

When the IMWG, which Dr. Rajkumar leads and which I'm a member of, redefined myeloma in 2013,

the SLiM-CRAB criteria were done to prevent the development of organ damage. That was the first step we took to say, why do we want the train to fall off the cliff? We want to stop the train when we know the risk of falling off the cliff is really high.

So since that definition change, we have gone back and validated patients who progress by SLiM criteria versus CRAB, and, in fact, you can't tell the difference. They are the same because the risk of progression is so high in the SLiM group. So it is a package deal. You get SLiM and you get CRAB together. You don't separate them out and say one does this and one does that, so one is more valid than the other. All of them together form the definition of multiple myeloma.

DR. KANAPURU: May FDA comment?

DR. VASAN: Yes.

DR. KANAPURU: I just wanted to comment on the point about some of the biochemical parameters required a confirmation of the test. I think it's important to note that this delay in initiation was

not just for those that had biochemical progression. We saw that even patients who had bone disease and disease progression based on imaging, there was a delay in initiation of treatment.

Again, I think the important thing here is, these patients, if the SLiM-CRAB criteria are what are used to diagnose multiple myeloma -- these are investigators who are starting treatment. Separate and apart from having a confirmation, we've seen if you think that there is a diagnosis of multiple myeloma, they get started on subsequent treatment. So here, we are seeing that investigators, despite having this SLiM criteria that is used for diagnosis of multiple myeloma, did not choose to initiate treatment.

And again, it was not just based on the biochemical parameters. Even those who had imaging progression did not initiate treatment soon after, which did not acquire confirmation. I just wanted to add that.

DR. CARSON: If we could just have another

comment to that.

DR. VASAN: Yes. I'll allow it.

DR. CARSON: Two other things. One of the things was FDA highlighted reasons for patients not getting subsequent therapy. The main reason that patients did not get subsequent therapy was a discrepancy between the local and the central labs. There's a local radiology read and a central radiology read. So that was the main driver of about 10 percent of the patients who are getting monitored very closely, still, and whether to initiate therapy or not.

Dr. Rajkumar wanted to comment further on this.

DR. RAJKUMAR: Vincent Rajkumar, Mayo Clinic. Since I was the first author of the 2014 International Myeloma Working Group criteria, I can clarify this. That paper was published in 2014 and this trial started in 2017. And for the first two or three years, there was reluctance among clinicians to accept SLiM criteria to start myeloma therapy. Today, of course, this is the accepted

criteria, and I expect patients to start therapy now.

But still, multiple myeloma is a disease which requires some judgment, so there are patients even today with newly diagnosed disease; not smoldering myeloma, even newly diagnosed disease, that we may wait a month, or two, or three, or longer to decide on starting therapy because we think the lytic lesion is too small and the patients' comorbidities are such that we want to see how far we can go. So I think that might explain why some of the patients were not immediately started on therapy.

But I think the main thing for me is that there were patients who were started on therapy. That's when the clinician made the judgment -- the investigator made the judgment that these patients need therapy. And if you look at that endpoint, 20 percent of myeloma patients required therapy in the dara arm and 40 percent at 3 years in the observation arm. The fact that 40 percent needed to actually start therapy by 3 years in the

observation arm shows you this is a high-risk smoldering myeloma group. The fact that 20 percent of the cohort needed to start therapy, even with daratumumab monotherapy, shows you that.

The final point is there was a point made that we expect in smoldering myeloma that there be a cure or there be a better outcome than even we've seen; yes, but that's when we start to use myeloma therapy, and there are trials going on like that, phase 1 and 2. But we didn't really truly anticipate that a single monotherapy would do better than the quadruplet that we used for myeloma therapy.

DR. VASAN: Ms. Powell?

MS. POWELL: I'm Joan Powell. I'm a patient advocate. I do not have myeloma, but I have a disease similar to it. It's called myelodysplastic syndrome. And as a patient, I want to say there are three points that I enjoyed, both sides. I wish other patients could be involved in something like this because a lot of times when you're a patient, you don't know why FDA approves this drug

and doesn't approve that drug. I took note on the quality of life. At the beginning, I was like, "Oh, okay!" And then the last presenter, I was like, "Oh, okay."

Then, diverse population, in my research -- I'm not a clinician or scientist -- I found that a lot of African Americans, Black people, have this smoldering multiple myeloma. Why wasn't this incorporated or why was the percentage so low at 2 percent?

And third of all, when you're a patient, it's all about, a lot of times, finance. Will this type of treatment be available for all ZIP codes, for all those on fixed incomes, or those that are multimillionaires? I don't know who wants to address my points, but thank you.

DR. CARSON: I can comment further just on the racial diversity of this study. It is true that the African American enrollment in this study was not as high as we would like it to be, but daratumumab isn't just used in this study but in a number of studies across the clinical development

program for daratumumab and in the real world since it's already been approved for 10 years.

What I can tell you is that we do have other studies that were not global studies but focused in on North America only, and in those studies, we did get higher African American enrollment for those patients. In particular, there were two frontline myeloma therapy studies, one, daratumumab in combination with VRd with transplant, and then one that was a maintenance study with daratumumab in combination with Revlimid. Those enrolled 16 percent African American patients and 22 percent African American patients. We did evaluate the data there and looked at white patients versus the black patients, and both in safety, efficacy, and in the PK of daratumumab, it was similar between both groups.

So while this one particular study didn't have as high of an enrollment because it was a global study, in the more focused studies, we have done that, and we haven't seen any differences for for ethnic patients.

DR. VASAN: FDA?

DR. GORMLEY: We'd like to respond to all three of your questions and comments, and I'll start with the last one. It's really not within the FDA's regulatory purview to consider cost, so we can't discuss that from our standpoint.

The first issue, at the FDA, we do draw a distinction between multiple myeloma and smoldering multiple myeloma. So while the applicant does have a good amount of data in multiple myeloma and diverse patient population, at the FDA, we do view this as a deficiency, the relatively low African American enrollment in this trial, given the greater prevalence of multiple myeloma, smoldering multiple myeloma, in African American patients.

I'd like to ask our colleague, Dr. Bhatnagar, to comment about the PRO.

DR. BHATNAGAR: Thank you so much. My name is Vishal Bhatnagar. I'm a medical oncologist, and I also am Associate Director for Patient Outcomes in the Oncology Center of Excellence. I have the privilege of looking at the patient-reported

outcomes data across all of the oncologic applications that come in.

For this application, to answer your question, I think the patient experience is extremely valuable, especially when it comes to things like tolerability: what are the symptoms or side effects from the treatment, especially when compared to patients who are not receiving any treatment at all.

In this trial, unfortunately, they asked patients only a handful of times in the first couple of years. So ask yourself how did you feel a year ago. A lot happens in that year. So I think we have to rely on what the clinicians provided in terms of the differences in terms of safety to get a better understanding of tolerability.

DR. VASAN: Dr. McKean?

DR. CARSON: If we could just have one reply to the PRO question?

DR. VASAN: Yes.

DR. CARSON: Dr. Rajkumar, if you'd like to

comment further on patient tolerability and the PROs from the study.

DR. RAJKUMAR: I think the two points are the PRO measurements were infrequent, and therefore you are not able to be sure of that. I think part is driven by the clinical fact that we used daratumumab regularly for full-blown myeloma along with other drugs, and we find it really well tolerated. So, that's a judgment call right now if you're not willing to accept the QOA study data that's there.

As far as the side effects go, which is a clinician's interpretation of that, patients with daratumumab, because they were getting evaluated far more frequently than the observation arm -- every week when they're coming in, and then the first few months -- all it takes is one fatigue, and it's counted. So yes, it looks like there are higher amounts of fatigue, a higher amount of this, but in our analysis, these adverse events are not only low grade mainly, but they're also time limited, usually constrained to the first

year, very typical for daratumumab.

DR. VASAN: Dr. McKean?

DR. McKEAN: Heidi McKean, Avera Cancer Institute, Sioux Falls, South Dakota. Can you pull up FDA slide 45, please? My question is for the sponsor, their response to this.

With the changing definition of the high-risk criteria, noted on this slide in the presentation by the FDA, it said half of the patients would be categories intermediate or low risk. And our question here today is whether Dara Sub-Q is a favorable benefit-risk profile for patients with high-risk smoldering multiple myeloma.

Are we overtreating some of these patients, or do you agree that we should really just focus on the very highest risk patients with smoldering multiple myeloma?

DR. CARSON: I'll have Dr. Rajkumar respond to your question, as he's an author on all of these different criteria. I think it may be more helpful to hear his point of view on this.

DR. RAJKUMAR: Except for the PETHEMA criteria, the Spanish criteria, all of the other papers I'm a lead author.

When the trial was designed, we did not have the MAYO 2018 criteria, and we developed the MAYO 2018 criteria to see if we can refine the population further. But when people ask me what is high-risk smoldering myeloma, we say any criteria that gets you that 40 percent/50 percent risk at 2 or 3 years is the high-risk group.

What we're trying to do is every criteria misses some of the patients who will progress in the first 2 or 3 years, so it's not only the people who are in the high-risk group that progress in the first 2-3 years. The stricter you make the criteria, the more people you will miss, and those people are not captured at all. So what criteria try to do is try to be as specific as possible while also being sensitive and not missing. For example, the IMWG 2020, the one that you see high at the very end on the right-hand side, that's just 9 percent of all smoldering myeloma patients, and

we know a lot more progress in the first 2-3 years.

So, yes, the criteria evolve like they always do and like it always does in every oncology indication. But we expect patients to have a choice so they can make shared decisions with physicians and decide if their risk is high enough to qualify for an intervention, if it was available. Without an approved indication, it's not going to be affordable either, so an approval is important for that, too.

DR. KANAPURU: Dr. Vasan, can we comment?

DR. VASAN: FDA?

DR. KANAPURU: Hi. I'd just like to comment. The indication that the applicant is requesting is for patients with high-risk smoldering multiple myeloma. And we acknowledge that this trial was initiated in 2017, but we have to reevaluate the results in what we currently understand.

As you've heard, there've been multiple changes in the disease definitions, and there's been evolving, not only the treatment landscape,

but also just understanding about what is smoldering multiple myeloma. I think it's really critical that you have a patient population where the benefit of the treatment overrides the risk. I think that's why most of these criteria are being developed, to identify a patient population that is at a sufficiently high risk that they would benefit from intervention, whereas avoiding overtreatment in those who are at a lower risk.

So currently, most of the criteria that were used in the AQUILA trial were based on individual criteria that were evaluated based on progression prior to 2014; multiple myeloma criteria were updated.

I would like to go to slide 139, and I don't agree completely that the high-risk patient population in the AQUILA trial, the progression was the same as the MAYO 2018. If you see on the slide, clearly the PFS improvement is most seen in the high-risk MAYO 2018 criteria. In the intermediate and low risk, there is some improvement but, again, the observation arm, the

risk of progression is low.

These patients who are considered high risk have a two-year progression risk of about 50 percent, but that's not what you see when you actually look at the AQUILA trial. Even at 5 years, nearly 50 percent are still progression free and, again, the results are most profound in the MAYO 2018 high-risk subgroup.

DR. VASAN: Thank you.

We will take a quick 10-minute break right now. We will start at 3:36. We do have a full group of speakers for the OPH session. Panel members, please remember there should be no discussion of the meeting topic during the break. Thank you.

(Whereupon, at 3:26 p.m., a recess was taken, and meeting resumed at 3:38 p.m.)

Open Public Hearing

DR. VASAN: Welcome back. 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 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 you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the industry group. For example, this financial information may include the industry group's payment of your travel, lodging, or other expenses in connection with your participation in the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address the 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.

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

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

MR. HANSON: Good afternoon. I thank you for the opportunity to testify in support of

providing high-risk smoldering multiple myeloma patients access to DARZALEX FASPRO. I have no conflict of interest, but the sponsor did pay for my travel to be here today. My name is Brad Hanson, and I am a survivor of multiple myeloma. I just completed 5 months of therapy using DARZALEX FASPRO and also a stem cell transplant. I'm out 3 and a half months.

Living with cancer is stressful, but living with high-risk smoldering multiple myeloma is even more stressful. Enduring the uncertain future, along with lab testing every 3 months, takes an emotional and often physical strain on the patient, and especially the families. That's why I'm here today to provide my support for approval of DARZALEX FASPRO for high-risk smoldering multiple myeloma patients.

Since my diagnosis of high risk in 2020, I waited for a treatment plan other than watchful waiting, but none existed. Instead, I felt as though I had an IED strapped to my body and a man following me around 24 by 7, 7 days a week, with a

plunger, waiting opportunity to push the button, and then I would go active. The mind monsters are always with you, torturing you with the unknown. Will I go active? Will I be able to see my grandchildren graduate from high school or even, for that matter, be born? What will my wife do without me?

Even though they're great therapies that exist and have great progression-free survival rates, you're still faced with the unknown future until you go active and someone provides you with a risk stratification and a treatment plan.

I lived in limbo like this and anguish, waiting on each lab test to be completed. The uncertainty and stress ultimately drove me into depression. My faith provided a way out, but there are a lot of people who don't have that way out. When you're diagnosed with high-risk smoldering multiple myeloma, you ask, "What can I do now? What treatment can I take? How can I avoid the toxicity associated with multiple myeloma treatment? What's the best thing for me now?"

Watchful waiting is not a comforting treatment plan. Having the option to be treated early with DARZALEX FASPRO as a high-risk smoldering multiple myeloma patient is going to change the emotional landscape. I strongly recommend that this committee approve DARZALEX FASPRO for the use of high-risk smoldering multiple myeloma patients. Our hope is in your hands. Thank you for your attention.

DR. VASAN: Thank you.

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

MS. LAVIN: Hello. Good afternoon. My name is Louise Miller Lavin. I'm representing myself as a high-risk smoldering myeloma patient. I volunteer as a myeloma coach for HealthTree Foundation, which is a myeloma advocacy foundation. Professionally, I'm an advanced practice psychiatric nurse and a licensed professional clinical counselor with a special interest in the emotional aspect of physical illness. I do not

have any financial interest in the outcome of this committee.

My introduction to myeloma began in May 2015. During a routine physical examination, I learned that my lab work was abnormal. I was asked to see an oncologist, who then referred me to a myeloma specialist. I was diagnosed with high-risk smoldering myeloma, and I truly felt that my world had collapsed and that I would not survive. I experienced a variety of emotions, including anxiety, shock, disbelief, helplessness, hopelessness, grief, anger, and despair.

Although I knew little about myeloma, I thought my best chance for a positive outcome was to receive immediate effective treatment. Clearly, I was very disappointed when the watch and wait method was recommended to me because I saw it as a system of monitoring, but not treatments. I then pictured myself as a pot of water simmering on the stove, and if it was not watched carefully enough or frequently enough, the water would boil over. I did not want this to happen to me in terms of my

myeloma. I was very worried about this treatment approach, so I decided to seek a second opinion.

I met with the chief of myeloma at a large cancer center, and I believed that this consultation actually saved my life. He explained to me that my light chains were extremely elevated, and without treatment, they were rapidly increasing. He actually shocked me when he said that I would have active disease within 8 months, and I could, if I wanted to, begin treatment immediately. It took me no time at all to make that decision. I knew there were pros and cons, but for three main reasons, I opted to begin treatment that week.

The first one, I wanted to regain control over my illness and my health. I did not want to be a passive victim of myeloma. Emotionally, I thought I would feel much better if I began treatment and was doing something active to stop my progression of my disease. Also, I thought I might do better with treatment in terms of handling it if I felt healthy, rather than later when I might be

ill from more advanced disease.

I feel very, very fortunate that early treatment was offered to me. It has been almost 10 years since I had my last treatment, and I have never progressed to active disease. I have been consistently MRD negative, I've never developed any lytic lesions, and I've had no organ damage. I actually perceive myself as a healthy, active individual, not as a cancer patient, but as a person with a chronic disease.

The reason I'm sharing this personal information -- I'm usually very private about my illness -- is that I am hopeful that early treatment will be made available to the high-risk smoldering myeloma population. I believe early treatment will delay and maybe even prevent their movement toward active disease. This would be a great gift to them and greatly improve their quality of life. Thank you for your consideration.

DR. VASAN: Thank you.

We have eight more speakers, so I'll be indicating at the 30-second point.

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

DR. RUBIN: Hi. My name is Jeffrey Rubin. I don't have any relevant financial interests, but I do have high-risk smoldering multiple myeloma. There's a strong history of myeloma in my family. My father and uncle had multiple myeloma. My mother had Waldenstrom's macroglobulinemia.

In November 2022, I had a SPEP test that detected IgA kappa and IgG kappa M-spike proteins, with a combined concentration of 0.9 grams per deciliter. A bone marrow biopsy showed approximately 20 percent myeloma cellularity, and FISH revealed several cytogenetic abnormalities, including a chromosome 4;14 translocation, 1q gain, and 13 monosomy. Each of the first two changes is an independent predictor of aggressive disease that responds poorly to current treatments for full-blown multiple myeloma, and 13 monosomy is thought to exacerbate the impact of 1q gain.

A subsequent PET-CT scan showed no evidence

of any lesions. My hematologist/oncologist told me that I had high-risk smoldering multiple myeloma, but he could not offer me any therapy because the standard of care for this condition is surveillance. However, he also advised me to seek enrollment in a clinical trial because the prospects were ominous if and when I progressed to active disease.

I entered a clinical trial at the NCI that combined an intensive phase of daratumumab, carfilzomib, and dexamethasone, with a maintenance phase of daratumumab alone. Happily, after 8 cycles of the 3-drug regimen, a bone marrow biopsy showed no evidence of residual minimal disease by flow cytometry, and PET-CT and MRI scans also were negative. The same encouraging results were seen after 12 cycles of daratumumab. The tests will be repeated at the conclusion of the trial when I will have received 24 cycles of daratumumab.

I consider myself lucky to be receiving treatment at an early stage of the disease process.

Given my strong family history, it's extremely likely I would have eventually developed active disease. By receiving treatment early on, chances are that I'll have a good quality of life for a longer period than if I waited for the onset of full-blown multiple myeloma.

I also am lucky because I live near a medical center that had a clinical trial for high-risk smoldering multiple myeloma

DR. VASAN: Thirty seconds.

DR. RUBIN: More research should be done to optimize the timing of treatment for people with this condition. Nonetheless, I firmly believe it is worthwhile to provide people with the standard of care treatment option such as daratumumab monotherapy that they could choose based on personal and medical factors. Thank you.

DR. VASAN: Thank you.

Speaker number 4, please state your name and any organization you're representing for the record. You have 3 minutes.

MS. VALLEFUOCO: Hi. My name is Kathleen

Vallefuoco, and I have high-risk multiple myeloma. I've traveled a long way to share my story with you today. My travel was supported by the sponsor, but my time is not being reimbursed.

I was diagnosed several years ago after lab results from an annual physical showed that I had elevated protein level. I was referred to a hematologist/oncologist. While in the doctor's waiting room, I kept looking around and thinking, "Wow. All these poor people are here for cancer treatment, and I'm just here because of some irregularity in my blood." When I met with the doctor, he informed me that I had something called MGUS, and that we didn't have to do anything right now. We would just watch and wait. He then gave me a brochure and sent me on my way. Phew!

When I got home, though, and I read the brochure, I learned that I had a precursor for multiple myeloma, bone marrow cancer. My first thought was, "Wait. He never used the word 'cancer.' What a chicken." I then went online to research multiple myeloma and learned all kinds of

very scary information, including that it is not curable, and that at that time, I had a 2 to 5-year survival rate. I was petrified.

We didn't have to watch and wait very long because my MGUS progressed quickly into smoldering multiple myeloma, and then progressed again into active multiple myeloma just a few months after that. I was starting down the road towards, first, one stem cell transplant, and after a couple of years, a second stem cell transplant and various courses of cancer treatment between and since.

Treatment has been nearly continuous and necessitated me dealing with various toxicities. It's been, and continues to be, a very difficult and scary journey for me and for my loved ones. I vividly recall accidentally finding a draft of an essay my daughter had written describing her pain knowing that her mother had incurable cancer. I even had to retire early from my career due to my medical health.

I've looked back often on the time of my diagnosis and thought, "Isn't the value of catching

a cancer diagnosis early, that you can intervene and hopefully delay, or even possibly eliminate the progression of that cancer?" I'd even asked my oncologist that question when I was first told that I now had smoldering myeloma and was told that no treatment was available --

DR. VASAN: Thirty seconds.

MS. VALLEFUOCO: -- at that early stage of multiple myeloma. I very much would have liked there to have been.

My hope is that others following in my footsteps have the opportunity to potentially delay the progression of this horrible disease and its multiple toxicities with treatment. Thank you for listening.

DR. VASAN: Thank you very much.

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

DR. GHOBRIAL: Thank you for the opportunity. My name is Irene Ghobrial. I have not received financial support from the sponsor of

this presentation.

I'm a Professor of Medicine at Dana-Farber Cancer Institute. I'm a physician scientist working in the field of myeloma for over 20 years. Over the last 10 years, I've focused both my clinical and lab work on early detection and interception of myeloma. In our clinic, specifically focusing on MGUS and smoldering myeloma, we follow over 4,000 patients who come to see us from national and international sites. I have led several clinical trials focusing on high-risk smoldering myeloma.

On behalf of all of our patients, I would like to strongly advocate for the approval of daratumumab in high-risk smoldering myeloma. I will specifically focus on three reasons.

The first reason is that smoldering myeloma is a real cancer. This is not MGUS. It's not DCIS. This is not a precursor state. This is a true cancer, but still asymptomatic. Just like stage 1 and stage 2 breast cancer, the cancer cells are truly malignant and are mature genomically.

There is nothing premalignant in smoldering myeloma. Waiting for further cancer progression and genomic evolution until patients develop fractures in their bones or renal failure only harms our patients because it allows for evolution and drug resistance. It is like waiting for metastatic cancer to happen before we treat our patients.

The second reason is that we cannot truly predict disease progression before end-organ damage occurs. I have seen hundreds of smoldering myeloma patients at my clinic, and we watch them very carefully. But even in the best practices, we cannot predict who will develop renal failure or fractures.

For example, two years ago, one of my patients with light chain smoldering myeloma started to show some light chain progression. Within 3 months, his light chain increased from 400 to 9,000, and he was in acute renal failure requiring admission to the hospital, dialysis, and urgent induction of myeloma therapy.

Unfortunately, he passed away being unresponsive to standard of care.

My third reason is that the criteria of defining high-risk smoldering myeloma may change, but the true definition is that patients progress within a few years to overt myeloma, and this is what truly the AQUILA study showed. We will continue improving our risk stratification just like we do in other cancers and just like we do with overt myeloma; however, we do not withhold therapy from patients until we reach perfection in risk stratification.

I would like to thank the ODAC members for their consideration and strongly advocate for the approval of daratumumab in high-risk smoldering myeloma. We owe it to our patients to give them the best care and improve their lives. Thank you.

DR. VASAN: Thank you.

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

MS. YOUNG: Good afternoon. My name is Anne

Quinn Young, and I am Chief Mission Officer at the Multiple Myeloma Research Foundation, where I've worked for almost 23 years. I'm speaking today on behalf of the organization and the hundreds of thousands of patients, caregivers, and families we serve.

The MMRF is a national 501(c)(3) and is the largest private founder of myeloma research. We receive support for research initiatives and educational programs from nearly every company with a myeloma program, often in the form of cost sharing and/or grants.

The mission of the MMRF is, and has always been, to accelerate a cure for each and every patient. As a patient-founded and focused organization, everything we do as an organization prioritizes patients over anyone else. We support the development of safe and effective treatments for patients at every stage of their disease on the path to a cure, including those with high-risk smoldering multiple myeloma.

One of the most significant unmet needs in

the field is a model to accurately identify smoldering patients. As we've heard today, we're at high risk of progressing to active myeloma within 2 to 3 years. Several recent studies have shown encouraging results in delaying progression from high-risk smoldering to active myeloma, in particular AQUILA; however, although predictive models for high-risk smoldering myeloma have incrementally improved in recent years, the data for trials in this population suggest that a substantial number of patients were not likely to progress to active myeloma within 2 to 3 years.

Accurate predictive models will greatly enhance the design of clinical trials and ultimately inform treatment decisions with the goal of treating those at high risk with appropriate treatment, while sparing those who are not at high risk from potentially adverse effects of currently available therapies.

The development of a more predictive model for high-risk smoldering myeloma requires that the entire community -- that's clinicians, patients,

and, very importantly, pharmaceutical companies -- join forces to contribute resources to this effort. The commitment and active participation of all these stakeholders is crucial for success.

The MMRF suggests the FDA consider mandating all sponsors of trials in this population contribute samples, outcomes data, and financial support to address this critical need. Samples from phase 3 and other trials are unique resources, and sharing in a consortium could be paramount to answering this question. We have led several large collaborative initiatives like this in the past, and we look forward to the opportunity to again expedite such an important project.

Additionally, as part of our commitment to empowering patients in the myeloma community in pursuit of more equitable access to quality care and outcomes, the MMRF believes in providing patients with the resources and tools to evaluate treatment options and make the most informed decision for their individual situation, including

evaluating options for the management and/or treatment of high-risk smoldering myeloma. The MMRF is strongly committed to educating both patients and caregivers, as well as healthcare providers, about optimal treatment options and clinical strategies in all sessions.

Thank you to the committee for providing me with the time to present today and to the FDA for its long standing commitment to making safe and effective treatments available to myeloma patients at every stage of the disease over the last 20-plus years. Many of these treatments have been transformative, and most patients are enjoying a longer survival and better quality of life after their diagnosis than ever before.

DR. VASAN: Thank you.

Speaker number 7, please state your name and any organization you're representing for the record. You have three minutes.

DR. ANDERSON: I'm Ken Anderson and have been a researcher and caregiver in myeloma for nearly 50 years, and have no relevant conflicts to

declare. Myeloma was previously treated only when patients developed end-organ damage or CRAB hypercalcemia, renal dysfunction, anemia, and bone disease. But due to the development of novel agents, which in combination have achieved high rates of durable responses and favorable therapeutic indices, the International Myeloma Working Group redefined myeloma to include SLiM laboratory imaging features. This allowed for earlier diagnosis and intervention with effective therapies and improve outcome in myeloma while avoiding end-organ damage.

Today's ODAC is a logical extension of this remarkable progress achieved in myeloma to patients with high-risk smoldering myeloma. Smoldering myeloma patients have more than 10 percent plasma cells and no SLiM-CRAB criteria. Although the clinical and laboratory features that would define smoldering myeloma patients at high risk for progression have evolved since initiation of this AQUILA study, and they'll continue to be refined in the future, patients in the observation arm

progress with their frequency and timing, characteristic of high-risk smoldering myeloma.

I first identified CD38 on myeloma cells more than 40 years ago and have been very closely involved in the preclinical and clinical development of daratumumab to treat both relapsed and newly diagnosed myeloma. There's a long and extensive experience which establishes both its efficacy and adverse event profile in myeloma. Importantly, the rate of adverse events leading to discontinuation of daratumumab was very low in the AQUILA trial, confirming its safety profile in smoldering multiple myeloma.

With 5-year median follow-up, risk of progression or death was 51 percent lower with daratumumab than observation; PFS was 63 percent versus 41 percent; and nearly twice as many patients in the observation and daratumumab cohorts have begun myeloma therapy, in my view, indicating a very favorable risk-benefit ratio.

During my five-decade career in myeloma, the treatment paradigm and patient outcome have been

transformed due to the collaborate efforts of investigators, caregivers, industry regulators, and patients. Delaying progression of high-risk smoldering to active myeloma, once unimaginable, has now been achieved.

The AQUILA study establishes a new standard of care in high-risk smoldering myeloma, and the framework for its use as a control arm in future randomized trials will be directed to further delay and someday prevent the development of active myeloma. I thank the ODAC for its consideration and strongly endorse approval of this major advance.

DR. VASAN: Thank you.

Speaker number 8, please state your name and any organization you are representing for the record. You have three minutes.

DR. BHATNAGAR: Good afternoon. My name is Dr. Tina Bhatnagar, and I am a community-based medical oncologist in Wheeling, West Virginia. I do not have any financial relationships with J&J, though I do have relevant relationships with other

pharmaceutical companies that are not in the myeloma space.

I appreciate the opportunity to speak with you and advocate for the approval of daratumumab, a CD38-directed monoclonal antibody for the treatment of patients with high-risk smoldering myeloma. This drug is already a cornerstone treatment in the management of patients with frank multiple myeloma, and based on the results of the recent phase 3 AQUILA studies showing both the significant progression-free survival and survival benefit, may also be an effective treatment option in the high-risk smoldering myeloma space as compared to active monitoring, which is our current standard of care.

Since hearing of the AQUILA results of the 2024 Annual American Society of Hematology meeting, I felt confident enough with the data to prescribe daratumumab for my patients with high-risk smoldering myeloma and have had excellent results. Daratumumab is well tolerated and quick to administer in clinics since it is given as a

subcutaneous injection. As expected, I have seen marked reductions in my patients' blood-based myeloma markers, indicative of a favorable disease response.

The time-limited duration of daratumumab for high-risk smoldering myeloma is appealing to patients, especially since they understand that it can deter progression to multiple myeloma and the associated organ damage that is a hallmark feature of this disease.

Many patients with high-risk smoldering myeloma in my practice suffer significant anxiety about their disease and live in constant worry that they will progress to multiple myeloma and start having to take multiple drugs to achieve disease control. Active monitoring is not only anxiety provoking but also comes with many extra challenges that I have personally encountered, including patient compliance with the monitoring plan, as well as insurance denials for imaging modalities that are necessary, including PET-CT scans.

Once patients with high-risk smoldering

myeloma progress to myeloma, they often require treatment with multidrug regimens, which can be even more logistically challenging, particularly for patients living in more rural areas who must travel great distances to receive their care and for the elderly in whom myeloma tends to be more common.

I believe, and the data support, that early intervention in patients with high-risk smoldering myeloma alters the course of their disease and improves survival. In addition, daratumumab will alleviate patient anxiety and also save them from the additive toxicities of future treatments should they progress.

My current high-risk smoldering myeloma patients have already benefited from daratumumab, and I have no reservations about discussing this as a treatment option for my future high-risk smoldering myeloma patients. I strongly encourage you to approve daratumumab for high-risk smoldering myeloma. Thank you for your time.

DR. VASAN: Thank you.

Speaker number 9, please state your name and any organization you're representing for the record. You have three minutes.

DR. CHEDID: Hi. My name is Solly Chedid. I'm an MD. I have been an oncologist for approximately 20 years. I was previously at University of Texas Medical Branch in Galveston as an assistant professor. Twelve of my 20 years of practice have been in community oncology. I have no financial relationships to J&J, and I'm not being compensated in any way for testimony today.

A small but important part of my community practice is made up of patients who are of myeloma, both MGUS, smoldering, as well as multiple myeloma. The patient population that's defined as high-risk smoldering, there are several different ways to define that. I won't get so much into the science of that right now, but these patients have a small but real probability of transforming into multiple myeloma. Depending on which algorithm we choose or which model we choose, we can determine what is the relative probability. But for these patients who

are at high risk, the relative risk of converting to multiple myeloma, they're followed closely to try to catch it before it becomes a life-altering event.

Unfortunately, in all too many times, these patients either are not followed in an ideal fashion or their progression doesn't happen in a stepwise fashion, and they present with potentially life-altering complications. As a community oncologist, when I think of treating patients, specifically in smoldering myeloma, I think of almost a cost versus benefit evaluation. The cost on one side accounts for not only financial cost but also side effects of the medications, time and resources to the patient, as well as the society as a whole.

I currently have 4 patients who are currently being treated for high-risk smoldering myeloma because the probability of them converting to multiple myeloma is relatively high. So when I'm following these patients, over the years, I've had two patients that easily come to mind, who

despite relatively close monitoring -- and this is usually every 3 months where we do, potentially, imaging with lab work -- unfortunately, had really life-threatening complications that resulted from rapid progression to multiple myeloma.

One person who presented to the emergency department with renal failure leading to dialysis, requiring an extensive ICU hospitalization for a whole host of other medical complications, this was very costly, very traumatic to the patient, to the family. Presumably, if that patient had been treated earlier on with a relatively low toxic agent such as daratumumab, this patient would have, potentially, maybe even obviated the need for any dialysis.

Another patient presented with a pathologic fracture. Again, this was directly related to smoldering myeloma that had converted to a lytic lesion and resulted in full-blown myeloma. This resulted in an emergent surgery with resulting complications. This patient specifically had a DVT, had really life-altering complications

requiring extensive hospitalizations and rehab time.

So daratumumab, is it appropriate for all patients with smoldering myeloma? No, not by any stretch. Basically, it's contingent upon the medical community to define which patients are at high risk, which patients have a high risk of converting to multiple myeloma; treat those patients appropriately with a relatively low toxic agent that, fortunately, after about 6 months of treatment, these patients come in for a sub-Q injection and go home once a month.

So from a toxicity standpoint to the patient --

DR. VASAN: I'm sorry. We're at time now. Would you be able to sum up in 5 seconds?

DR. CHEDID: Yes. Basically, risk versus benefit, I think the benefit of daratumumab for high-risk smoldering myeloma is well worth the effort for most of these patients, in properly-defined patients. Thank you.

DR. VASAN: Thank you.

Speaker number 10, please state your name and any organization you are representing for the record. You have three minutes.

DR. TICKU: Hi. I'm Dr. Jonathan Ticku. I'm a full-time physician in community practice. I practice in western Wisconsin. I primarily serve a more rural patient population. I'm board certified in both medical oncology and hematology, and I've been seeing patients for over a decade in that area. I do not have any conflicts of interest and no financial interest either.

I'm here to discuss daratumumab in the high-risk smoldering myeloma population and provide perspective on behalf of real-world community oncologists and hematologists, along with the rural patient population that I serve.

In community oncology, in particular, we've had increasing time pressures over the last decade. The clinical limitations for follow-up are challenging. The NCCN guidelines are recommending 3-month interval follow-up for patients with smoldering myeloma, high risk; however, this is

increasingly difficult to accommodate in our rural oncology and hematology practices, given the lack of work force, which I do not see resolving anytime soon.

Additionally, the advanced imaging, such as PET-CT scan, is not readily available in those rural settings either. I've seen in my own clinic an avid pickleball player with smoldering myeloma and stable hematologic indices, on regular follow-up, develop minor back pain; and then this ended up being a very active myeloma progression with, essentially, significant spine involvement, ending his active lifestyle.

This highlights that some patients progress to significant bone lesions, even despite following guidelines with interval monitoring. The critical early intervention window can be lost in some patients that suffer from these irreversible bone fractures.

Patients in the rural setting often have goals of care that are vastly different than many of their counterparts in urban and metro settings.

I do know my patient population highlights the importance of low toxicity treatment options and puts value on quality-of-life extension.

With 10 years of experience treating patients with daratumumab, if we're in active myeloma, I find daratumumab is well tolerated. If available, I would consider offering the single-agent therapy for patients with high-risk smoldering myeloma, and I think it's a very valuable option and should be available for the select population of patients. Thank you.

Questions to the Committee and Discussion

DR. VASAN: Thank you.

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

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 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.

After I read each question, we will pause for any questions or comments concerning its wording.

DR. CARSON: Dr. Vasan, if we could just have one opportunity to respond to FDA's last slide that they presented?

DR. VASAN: I'm sorry. Out of respect for the our process and the additional discussion, we'll have to defer.

DR. CARSON: Okay.

DR. VASAN: We will proceed with our first question, which is a discussion question. Discuss how the differential results --

DR. SEO: I'm sorry. Could we have slide 4, please, for the afternoon session?

DR. VASAN: Thank you.

We will proceed with our first question, which is a discussion question. Discuss the clinical meaningfulness of the efficacy endpoints

assessed in the AQUILA trial.

Are there any issues or questions about the wording?

(No response.)

DR. VASAN: Alright. If there are no further questions or comments, we'll now open the question to discussion.

Dr. Spratt?

DR. SPRATT: Dan Spratt, UH Seidman, Case Western Reserve. I say this with Dr. Rajkumar here. I think these risk groups are phenomenal, but I think they're terrible for regulatory approval. These are prognostic risk groups; these are not predictive.

So what that leaves us with is we are seeing a signal -- and I'd actually disagree with FDA's comments earlier that the benefit is potentially restricted to high risk. I don't think that was shown in this data at all. So the problem is, we actually don't really know what is the subgroup that is really benefiting from this therapy because we heard comments earlier maybe this is not enough

therapy. So it's high risk. If it's not enough, then should we be approving just a monotherapy? What is this population? Basically, I don't know.

But going to the question here, the clinical meaningfulness, we're going to give patients, every single patient who meets these criteria, treatment, but in the active monitoring group, it looked like only 46 percent of patients, with the median follow-up you guys have, did not have a first-line therapy. We'll just call it half and half. So you're going to give everyone up front a therapy when half would never go on, at least with the follow-up you have, to first-line therapy.

It seems that you're wanting to give a therapy to prevent end-organ damage from myeloma. That wasn't shown in the trial. You want to give this therapy to improve quality of life. That wasn't clearly shown in this trial. The part that actually was the most impressive to me is that the trends have improved overall survival. And I would actually just say, personally, I disagree a little bit with the FDA that said the comment that

6 percent survival difference at 5 years is modest. I would think in an indolent disease, that's pretty profound, albeit the caveats of OS.

So I would say I'm -- as I'm sort of waffling here -- very torn here, and that many of the things I think we're trying to show that are meaningful were not demonstrated, but they're definitely some strong signals. And I'll just end with that I think anxiety from biochemical changes is a physician's failure to reassure patients. I think if patients -- we are in a fee-for-service model; that we are incentivized as physicians to essentially not fully reassure patients, and that biochemical changes you guys showed in the study do not always translate to harm.

So the fact that we heard pretty powerful statements from some patients today of how fearful they are when they have MGUS or smoldering myeloma, when they're both here today, and hopefully they'll continue to be with us for a while, I think that that alone, anxiety from biochemical changes, should not be the definition of clinical

meaningfulness, to me. Thank you.

DR. VASAN: Thank you.

Dr. Frenkl?

DR. FRENKL: I actually had --

DR. SEO: Dr. Frenkl, if you could turn on your mic, please. Thank you.

DR. FRENKL: I'm sorry. Tara Frenkl, industry representative.

Maybe Dr. Conaway can help us understand a little bit more. I was also, as Dr. Spratt was saying, just taken by what appears -- even though I understand that the PFS2 and overall survival are not statistically significant as set by the thresholds in the protocol, the HRs are quite impressive, I'll say, and the confidence intervals do not cross 1.

So can you help us with the kind of confidence that we should have in these endpoints?

DR. CONAWAY: Well, I think they were presented very well by both the FDA and the sponsor as to what the limitations were in those analyses; though for overall survival, there aren't that many

events, so it's difficult to to draw firm conclusions. But you can draw information about signals, about a 6 percent benefit in survival.

I think, in this case, all these endpoints have their limitations that were brought out in the discussions, but I also agree that there are some signals, if not statistical significance, in those analyses.

DR. VASAN: Dr. Lieu?

DR. LIEU: Yes. I agree significantly with the comments made by Dr. Spratt. It's crazy to say, with a follow-up time of 5 and a half years, that the data may be immature, but it might actually be a little bit immature here.

What I'm most interested in regards to the PFS curves -- and I certainly agree with this assertion that these are asymptomatic patients, we're giving them treatment, and the criteria by which they're "progressing," quote/unquote, is also kind of an asymptomatic criteria. But what I'm most interested in is the tails of the curves. The comment was made, is there a chance that some of

these patients may never progress to getting treatment for active multiple myeloma? And I think that time will tell. So, in some ways, I think the data need to mature a little bit more for PFS and OS, but I think that this signal is obviously real.

I do want to make the point that regardless of when you start treatment -- and you can say that 20 percent of the patient population didn't initiate therapy, that's true, but you're also saying that 80 percent of the patients are then moving on to triplet or combination therapy, and there's a quality of life and a treatment concern just from receiving those drugs in the active setting, so, to me, the PFS criteria is meaningful.

There's also a concern when you use this agent up front in smoldering multiple myeloma, then what is the efficacy in the frontline setting for active multiple myeloma? So you're looking at PFS2 to try and see if there's a detriment, and at least from that signal -- and I agree, PFS2 is very difficult to interpret, and there's some concern about even what they're receiving in the active

treatment setting. But you're not seeing a shortened PFS2 in the treatment arm, and I think that that is telling, that you're not, actually, at least in the data that we have, harming patients by giving them daratumumab in the smoldering multiple myeloma setting.

Then OS, we obviously want to see it, but I also agree with Dr. Spratt that I think we're seeing a positive trend. One of the concerns here that we're worried about is, are we harming patients with this therapy, and I don't see any evidence to suggest that that is the case. Thank you.

DR. VASAN: Dr. Spratt?

DR. SPRATT: Dan Spratt, UH Seidman, Case Western. Can you guys pull up table 10 from the FDA's tables? I don't know which slide it's on, but it's basically first-line subsequent therapies. Hopefully, that gave you a whole bunch of information.

But basically, to Dr. Lieu, I just want to make sure because I know what the FDA presented is

that 20 percent -- we'll say 80 percent went on to progress to multi-agent, most likely therapy. That's of people who progressed. So it's really -- if you do get it up, I have it in front of me, that it's 54 percent of patients in the control arm. Basically, the active monitoring arm went on to first-line therapy. So it's really you're giving everyone therapy versus half of patients will go on to get any therapy.

And if they pull the table up, some of these were single agent. I realize multiple or multi-agent therapy, not to say that should completely dissuade what you're saying, but it's not that 80 percent of all patients are going to get therapy in the first 5 years.

Sorry, were there any were there?

DR. VASAN: FDA, can you identify the slide number?

DR. GORMLEY: Yes. Is this the slide that you were referring to or from the briefing document slide?

DR. SPRATT: It's from the briefing -- don't

worry about it. It's ok.

DR. VASAN: Could we pull up that slide, please?

DR. SPRATT: There it is. At the top, it's 54 percent, and you can see of the drugs -- I mean, a handful, not that I know what all these acronyms are. I assume single letters are single drugs.

DR. VASAN: Great.

DR. MADAN: Ravi Madan, National Cancer Institute. Just to piggyback on this, kind of flip it to the other side, 100 percent of the 50 percent that won't progress at 3 years will get treatment. That's the other way to look at this as well. It's a difficult discussion with a lot of different perspectives, but that's the other side of the coin.

DR. VASAN: Dr. Conaway?

DR. CONAWAY: And I think the other part of that is that it's hard for me to judge. There will be, of course, people who receive treatment, progress, or don't progress, and have a side effect. And, clearly, they're not benefiting from

the treatment, and I'm trying to get a sense of what that proportion is to balance this risk-benefit.

As I see it, when we're trying to weigh risk, there are a couple. One is that you're treating everyone, and there will be inducing side effects, adverse events, in people who do not benefit. That's a risk. And then, of course, the risk that we talked about that's looked at with PFS2 is the risk that the treatment up front then limits the effectiveness of what seems like an effective therapy after people progress.

That second part doesn't seem like such an issue, but I'm really struggling with that first risk-benefit calculation in the light of the slides that were just shown.

DR. VASAN: Alright. I think I'll summarize here. Oh. Dr. Spratt?

DR. SPRATT: Sorry; one more. Dan Spratt, UH Seidman, Case Western. And I'm allowed to ask a question to them.

DR. VASAN: Yes.

DR. SPRATT: It's a very direct question to Dr. Rajkumar. Would you classify this condition, smoldering myeloma, as cancerous or precancerous? Very simple.

DR. RAJKUMAR: Vincent Rajkumar. Almost all patients with high-risk smoldering myeloma are cancerous, as Dr. Ghobrial mentioned. Genomically they're indistinguishable from multiple myeloma.

DR. SPRATT: So would this be classified as a cancerous condition, not a premalignant state?

DR. RAJKUMAR: It is not premalignant. It is asymptomatic, but not premalignant. It is cancer.

DR. SPRATT: Thank you.

DR. VASAN: Dr. Choueiri?

DR. CHOUEIRI: Hello, everyone. Toni Choueiri, Dana-Farber. Sorry I'm calling online. My question here, I'm struggling very, very much, perhaps more so than Dr. Spratt, with the decision here, very much so.

I just wonder, we do that in solid tumor. I do solid tumor oncology, and we approve drug based

on PFS. Sometimes there is no OS in the adjuvant setting. And we know after surgery, despite the high risk of recurrence of many solid tumors -- breast cancer, kidney cancer, bladder cancer -- a subset is cured with surgery only, or radiation, or chemoradiation. But we still give them the treatment, and we don't ask why.

I do wonder if we are being tougher on heme malignancies, in general, because we can monitor the patient with blood parameters, et cetera. But based on the eight folks that spoke, it seems that this is an imperfect monitoring despite the biomarker, the superior biomarker, testing that the myeloma folks came up with. Thank you.

DR. VASAN: Alright. I'll summarize here.

We had a lot of discussions about the clinical meaningfulness of these efficacy endpoints around PFS, PFS2, and OS, recognizing, I think, the the information it gives us but also the imperfections in these endpoints relative to myeloma.

There was discussion about what these

endpoints really mean. They're clearly prognostic, but are they predictive? There was recognition that while the goal, of course, is to prevent smoldering myeloma from advancing to multiple myeloma, it had not been shown that certain events like end-organ damage had been meaningfully decreased, of course noting that there was a small number of events. There was discussion for many of the patients in the open session about the anxiety that this patient population feels. But that also, a physician's job is to help allay that anxiety; that's not the job of the drug.

There was concern about perhaps a bimodal distribution of patients in this population, that some of these patients are getting overtreated. They will never progress to myeloma. Some of them are getting undertreated. They may have had myeloma based on the evolving risk criteria and also may be undertreated because they're getting dara monotherapy.

Now, we will move on to question 2, which is also a discussion question. Discuss the

benefit-risk of daratumumab hyaluronidase, Dara Sub-Q, for the intended high-risk smoldering multiple myeloma population.

Are there any issues with the questioning here?

(No response.)

DR. VASAN: And I realize I think we've covered some of this in the discussion, but we'll just continue. I'll add one thing.

Neil Vasan. This is piggybacking a bit on Dr. Choueiri's point. I think when solid tumor oncologists are thinking about this as what we're really measuring, there are examples of chemo prevention -- excuse me, not chemo prevention, but giving therapies in high-risk populations. We have tamoxifen that's approved. I'm going back and forth struggling to think, as Dr. Choueiri pointed out, are we harder on our hematology colleagues and these evidentiary standards.

I would like to ask the FDA if that is a helpful precedent, or a helpful evidentiary bar, for thinking about this issue, thinking about the

historical approvals of tamoxifen in a high-risk population. I think there are some similarities and some differences. I think those definitions are pretty fixed. I think they're not really controversial. The Gail Model is used for risk stratification.

How should we be thinking about this, in the same way or not? And does history change the way that we think about this?

DR. GORMLEY: Nicole Gormley, FDA. I think these are really important considerations and things that I think we struggle with when thinking about the impact, really, of intervention. I think there are some differences between solid cancers and heme malignancies. Depending on which specific setting you're referring to, I think there are some differences, twofold.

One, I think in terms of rates of progression, as we were just discussing, not all patients with smoldering multiple myeloma or high-risk smoldering will ultimately progress, so there are some differences. I think the other

issue is that certain solid tumors, in theory, with surgery, we're really talking about cure. So that may be different if you're talking about adjuvant therapy or whatnot. But I think perhaps, as well, the depth of response is something that we consider.

This has come up, though, just within the heme space in multiple areas. In the heme space, we've had a lot more discussions about maintenance therapy, and it's somewhat analogous, where you've already received your treatment in terms of transplant, or in terms of other, high-dose intensive therapies. And in that setting, especially in heme malignancies, even in myeloma, there have been challenges with demonstration of an improvement in overall survival, but I think that's a little bit different.

There are some in the myeloma field, when they're talking about maintenance therapy, that really strongly advocate for overall survival, and there are others that say that it may not be feasible to rely on overall survival, and then look

at a progression-free survival endpoint instead. I think the difference and some of the challenges extrapolating the maintenance setting to this setting, in myeloma even, is that, again, we don't have as much data, or any data really, looking at PFS as it's defined in this early smoldering setting and its relationship with long-term outcomes; whereas in the maintenance setting, we have a little bit more data to suggest that relationship.

So here, this really is just progression-free survival as delay in diagnosis of multiple myeloma, and I think we heard multiple discussions already about the clinical meaningfulness of that. So I think there are some challenges when considering endpoints in one setting versus another. And even between solid tumors and heme malignancies, I think it's a little bit challenging to assess how meaningful those are based on that.

I don't know if others want to comment.

DR. KANAPURU: Thank you. I think,

obviously, there are differences between solid tumors and heme malignancies. Again, for the DCIS, the surgery is done, and then tamoxifen is given afterwards. But I think even looking within heme malignancies, we have disease conditions, like even CLL, like follicular lymphoma, but you don't treat even when you have a diagnosis. They're treated when there is a risk of having a significant event.

So it's not just in heme. There is a precedent that you don't treat just because you have the disease. I think all the more, one thing that we are trying to -- it's difficult. I can understand just from the discussion that it's really challenging to see what the benefit-risk is. I think that's where having a patient population that's sufficiently high risk and that has the risk of progression, identifying the patient population, and maybe the benefit-risk is more clearer in that patient population, and I think we're struggling a little bit with that here.

DR. VASAN: Thank you.

Dr. McKean?

DR. McKEAN: Heidi McKean, Avera Cancer Institute. It's actually been a shift in focus for me, reading, listening today, listening to Dr. Rajkumar, and listening to the other physicians online, thinking of smoldering multiple myeloma as being a malignancy, and that we're just waiting and watching for a metastatic disease to show.

I guess what I'm still struggling with, though, is if we're really preventing cancers or if we're just delaying cancers being diagnosed. And when we intervene, we're recommending lifelong therapy started earlier, so that lifelong therapy better be not increasing toxicity and not harming their quality of life. So that's still the space that I'm struggling with the data presented today.

DR. VASAN: Dr. Madan?

DR. MADAN: Ravi Madan, National Cancer Institute. As Dr. Lonial alluded to earlier, we actually face this in prostate cancer. And I don't want to speak for Dr. Spratt, but this inspired his sense that biochemical biomarkers are the responsibility of the physician to explain to

patients and help with education, and I agree with that. I think that in prostate cancer, the FDA did approve based on a biomarker metric that's more predictive than prognostic, which is PSA doubling time, the combination of hormone therapies. And the field has widely split in terms of the value of that and whether or not it's actually being used.

I don't necessarily think this is us being harder. With respect to the FDA and not meaning to disagree, I don't think it's a matter of us being different than heme malignancies or with solid tumors. On the contrary, every meeting you go to talks about ctDNA. Well, ctDNA is going to do this in every solid tumor, too, eventually, if the technology gets right, and you'll be having this discussion for every disease state. Getting it right now may be important to how we do things in the future. But, again, I think we just have to ask ourselves, just because we can treat, should we?

DR. VASAN: Dr. Spratt?

DR. SPRATT: Dan Spratt, UH Seidman, Case

Western. It's sort of a slippery slope thinking what's next. The agents that are in multiple myeloma seem very active, so, obviously, the next trial is this. Let's say if this is approved, it's going to be a multi-agent regimen, and a precedent will be set that we're delaying the development of multiple myeloma.

So at what point -- because that incremental toxicity -- because you'll already say, fine, daratumumab toxicity, we're saying it's ok. We're going to layer on, we're going to layer on, we're going to layer on, and probably each incremental layer will be modest.

It's a very, very slippery slope, and that's why I still go back to -- unfortunately, it would be great. I think one of the open public comment speakers from, I think, the Myeloma Foundation said can the trial data be given to foundations or people to analyze? Because I really think they need to define a predictive, much better risk grouping system for regulatory approval, not just for prognosis, to really hone in, because,

inevitably, as I think multiple panel members said, we're going to overtreat patients. And then when you go on to the doublet, triplet, quadruplet, you're going to really overtreat patients.

But I think to your point, Dr. Vasan, that's why it's very reassuring to me what was said, that this is not premalignant to malignant. This is, basically, malignant to a more aggressive malignant form. So that's where I think these benefits may be more meaningful.

I think Dr. Lieu's comments were excellent. I think a couple more years of follow-up, to me, would be extremely valuable. I still think that overall survival signal, to me, is very profound, and I think with a little more follow-up, that may seal the deal in my eyes.

DR. VASAN: Thank you.

Dr. Frenkl?

DR. GORMLEY: Can I ask a question, actually, as well first?

DR. VASAN: Yes.

DR. GORMLEY: Actually, I want to ask a

question to Dr. Rajkumar, and I wholeheartedly recognize that this is a continuum.

Can you comment on answering Dr. Spratt's question as it relates to MGUS?

DR. RAJKUMAR: So MGUS is the classic premalignancy just like the polyp. Smoldering myeloma is not that. And we've done many genomic studies independently, both with Dr. Irene Ghobrial, and she's doing her own stuff, and we've been doing it separately as well.

When you assess -- and the reason why we are even talking about CRAB features is because, for years, we have never been able to distinguish when a patient's bone marrow has, say, 40 percent plasma cells. Are these malignant or not? In every other cancer, they will call it malignancy and sign it out as adenocarcinoma breast. But here, because we are not able to distinguish the premalignancy from the malignancy, there was a doubt about how are we sure without end-organ damage?

So fundamentally, this is the only cancer in which there's a requirement for a clinician to say

there's hypercalcemia before you call it a malignancy. That has now changed with genomics. When we look at it, high-risk smoldering myeloma, in fact, even low-risk smoldering myeloma, vastly, almost all of them, have the same malignancy signatures. And if you follow these patients long enough -- this is only 5-6 years follow-up; the QuiRedex has now gone on for a much longer term follow-up -- virtually nobody in the observation arm has not progressed.

Everyone progresses eventually, and that's what I meant when I said, if you follow them long enough, everyone will progress. Early intervention for 3 years prevents the patients from getting the full-blown myeloma therapy, which is a guarantee. And you've already seen that at 3 years, 20 versus 40 percent.

DR. GORMLEY: I just want to highlight, though, to the comments that have been made earlier, I think that this, to an extent, really does underscore the need for better identification of patients. It's a continuum in terms of

high-risk smoldering, intermediate low risk, MGUS. And these patients are being identified as similar based on genomic features, but those are present in low risk, intermediate risk, and throughout. So, again, just highlighting that I think there is a need for better identification of patients that are more likely to progress.

DR. VASAN: Dr. Frenkl?

DR. FRENKL: Thanks. Just a comment on the question a little bit here. For me, the benefit is clear. I mean, the study met its primary endpoint. ORR is highly significant as well. We've talked about the likely clinical meaningfulness of OS and PFS2 as well. This is a very long study, so the field has evolved, which is great. We want that for patients. With that, I think we also heard how these criteria will lead to end-organ damage. So we're saying that none of it maybe didn't develop in the study, but we heard earlier that all of these criteria have really significant clinical relevance in terms of getting us there.

So I think given where we are, and the

change in the landscape, and taking everything into consideration, if this drug is approved, all of the data will be available, and it will be in the label as to what was in the study.

Also, we heard a very clear need, for me, from the experts, as well as from patients. So given the data and the positive studies, and again, that was agreed upon with the population and the endpoints when it was developed, that we let the physicians and the patients decide if they're going to take the drug or not.

DR. VASAN: Dr. Spratt, were there any other comments?

DR. SPRATT: I'm good. Thank you.

(Laughter.)

DR. VASAN: Alright.

To summarize, there have been several important points brought up. The first is the question of are we preventing disease or are we delaying disease? There was a robust discussion about comparisons with treating smoldering myeloma like we think about adjuvant therapy or precursor

conditions in breast cancer, prostate cancer.

There were, I guess, calls to the field to help create a biomarker if we're considering this malignancy. I think there was a great discussion among all of us -- ODAC, FDA, and the applicant -- about where is smoldering myeloma in this continuum between MGUS and between active myeloma, and I believe those are the things we discussed.

So, if there are no further questions, we will proceed to question 3, which is a voting question. We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote, and if you are unsure of your vote or wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the

vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to. We will continue in the same manner until all questions have been answered or discussed.

Question 3, the voting question, do the results from the AQUILA trial provide sufficient evidence to support a favorable benefit-risk profile for Dara Sub-Q for patients with high-risk smoldering myeloma?

Any concerns about the wording of the question?

(No response.)

DR. VASAN: Alright. If there are no further questions, we will begin voting.

(Voting.)

DR. SEO: This is Jessica Seo, DFO. For the record, the results of question 3 are as follows: 6 yeses, 2 nos, and 0 abstentions.

Dr. Vasan?

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

Dr. Choueiri?

DR. CHOUEIRI: Hello, everyone. Toni Choueiri from Boston Logan Airport.

(Laughter.)

DR. CHOUEIRI: I have to say, again for the second time of the day, this was a very tough decision for me, tougher than the morning session. I listened carefully to the sponsor, to the FDA. I did my homework. And I listened to the patients, who are the real heroes here. I listened to some of the best key opinion leaders in myeloma I have the utmost respect for.

I have some concerns. Despite the differences in progression event, the risk of severe complication was similar between the two groups. I also have concerns about the high-risk in the AQUILA study that, as we discussed, they

differed from the MAYO 2018 criteria. Only 40 percent of enrolled patients were classified as high risk, so we may be overtreating patients that have MGUS for 3 years, and we may have some real multiple myeloma patients that we are undertreating.

But the thing today is that we do not have, today, an ideal classification on whom to treat for sure, with high certainty. What sealed the deal a bit to me is I could not ignore the trend in OS with a hazard ratio of 0.52. Despite this is premature, there's a long follow-up; therefore, I would advocate for daratumumab for high-risk smoldering myeloma.

And therefore, for the specific question, in high risk, do the results from the AQUILA trial provide sufficient evidence to support the favorable benefit-risk profile for Dara Sub-Q for patients with high-risk smoldering multiple myeloma? For this question, my answer is a yes. Thank you.

DR. VASAN: Dr. Spratt?

DR. SPRATT: Dan Spratt. I voted yes. I think that my vote comes down to all the endpoints effectively are favoring the intervention here. I think because this is cancer, as a malignant condition, albeit maybe at an earlier stage, my concern initially is this is maybe chemo prevention. This is something that is a real entity with high rates of progression. I think the survival differences are meaningful. Although it's still a signal, I think with longer follow-up --

So, to me, what I would implore the FDA is that, number one, the high-risk definition is somehow defined. I know the FDA likes to use trial eligibility criteria, which has been a problem in history when you don't see a signal and subgroups, as we'll maybe discuss soon and in different context.

I would implore the sponsor that this data, A, continues to be followed so that OS data can report out; and as well, as I already mentioned, that this data becomes available for further understanding for optimal risk stratification so

that when you add on multiple drugs in this setting, which will be inevitable, that we can have a stronger more enriched group. But those are my comments.

DR. VASAN: Neil Vasan, NYU Langone, and I voted no. This is a really tough decision. This was a very well-designed trial, and I really commend the applicant and the FDA for a very robust discussion. I think in the words of Dr. Gormley, this is uncharted territory regarding the endpoint.

I think, for me, the reason I voted no was that I felt that this bimodal distribution within the population, that there are a group of patients, that we're overtreating a group of patients, that we're undertreating. We don't really have great data right now to understand who those people are, so that drove my vote.

I agree with Dr. Spratt's comments about if this does result in approval, to have clear indications in the package label about how this is thought of and how we think about high risk. And thank you today, also, for the 10 speakers at the

OPH discussion. We really appreciate all your comments.

MS. POWELL: Joan Powell. I voted yes because, as a patient, I tell everyone you have to advocate for yourself. Sorry about my voice. It gives us another option. We make the decision whether or not we will be involved in this, taking this additional drug. Thank you.

DR. CONAWAY: Mark Conaway. I voted yes for a couple of reasons. I don't think there's any doubt that there is a high-risk population for whom the benefits outweigh the risks. Even if we don't know exactly what that population is at the moment, I'm confident that there will be some resolution of that.

The other is, listening, particularly in the open public session, risk is such a personal perception, a personal decision, that I do see a sizable portion of a population whose perception of benefit would outweigh the risk, even apart from what we see in the data today. So there is a population for whom the benefits definitely

outweigh the risks.

DR. MADAN: Ravi Madan, National Cancer Institute. I voted no; and, again, noted on the question of benefit-risk, not necessarily approval. That's a separate issue, not part of our purview. But I do want to compliment the sponsor for running, really, the most correct trial possible at the time the trial was launched with an observation arm. And I'm sad to hear that will never be done again because look at this robust discussion and great conflict we had when observation was the arm.

For me, it was kind of a math question. We're probably overtreating more than 50 percent of the patients at 3 years. Of the patients getting treated, 40 percent of them are having grade 3-4 toxicity. And that didn't translate to any real clear signal in PFS or overall survival, clouding my view of what the early treatment is really doing.

I'm probably overly biased because in prostate cancer, overtreatment is the order of the day based on biomarkers. And it's actually not

better with approvals; it's worse because that's how you relieve anxiety, in one way, without having to explain things away.

But as I said earlier, I think this is going to be a broader issue across all of oncology. We're getting better technology every day. We're getting more opportunities to treat earlier. And I think, again, we have to really step back and ask ourselves, just because we can treat earlier, should we? I have to say that the data is interesting, but the benefits here of early treatment are not completely clear. So that's why I answered the question the way I did. Thank you.

DR. McKEAN: Heidi McKean. I answered yes. As I shared before, the shift for me was thinking of smoldering multiple myeloma as a malignancy and allowing the physician and patient to look at this data and intervene earlier if they so choose. But I would challenge the people that write the trials -- because there will likely be more, as we heard, agents added to Dara Sub-Q -- to be sure that we are not overtreating these patients.

DR. LIEU: This is Chris Lieu, and I voted yes. I do believe that the benefit-risk profile is positive. I think it's kind of marginally so. So make no doubt about it, this is going to lead to overtreatment for a population of patients, and those patients may experience toxicity, particularly infection from this.

But what weighed heavily on me were two things. I think, number one, I really want patients and providers to have the option to discuss this, to have the benefit-risk discussion, and I think that's a very nuanced conversation. I think that conversation includes the fact that there are toxicities from this drug, but there's a chance that you can prevent a life-altering fracture; that you might be able to prevent, or delay at least, the onset of treatment; that you might be able to delay or prevent end-organ damage. I think that is a conversation that I want patients and providers to have the option to have.

Then the second thing, to Dr. Spratt's point, this really can't be the end of the story.

This is going to lead to overtreatment. There has to be a predictive biomarker or some type of risk stratification to refine this group. And I don't think we have a lot of interest, to Dr. Spratt's point again, of just adding more agents and getting a marginal increase in progression-free survival with significant added toxicity. I don't think that that would be a good outcome.

I also just want to say thank you so much to the FDA and the applicant for, honestly, just wonderful presentations today.

DR. VASAN: So, before we adjourn, are there any last comments from the FDA?

DR. GORMLEY: Yes. I just want to thank everyone for their time and really thoughtful deliberations. Internally at the FDA, I'll just share it's really nice to hear that we're not the only ones that struggle with some of these issues. So we really appreciate all of your thoughtful feedback and all your comments today. And thank you to all the patients, as well, for speaking today. Thank you.

Adjournment

DR. VASAN: We will now adjourn the meeting for today and continue for the next session tomorrow at 8:00 am. Thank you.

(Whereupon, at 4:56 p.m., the afternoon session was adjourned.)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Morning Session

Wednesday, May 21, 2025

8:00 a.m. to 11:23 a.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Jessica Seo, PharmD, MPH

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

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(via video conferencing platform; May 20 Sessions Only)

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Professor, Harvard Medical School

Dana-Farber Cancer Institute

Boston, Massachusetts

Mark R. Conaway, PhD

(All Sessions)

Professor, Division of Translational Research and Applied Statistics
Department of Public Health Sciences
The University of Virginia School of Medicine
Charlottesville, Virginia

William J. Gradishar, MD

(May 21 Sessions Only)

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

Ravi A. Madan, MD

(All Sessions)

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Head, Prostate Cancer Clinical Research Section

Genitourinary Malignancies Branch

Center for Cancer Research

National Cancer Institute

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P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

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

My name is Dr. Daniel Spratt. I'll be chairing this meeting. I now call the morning session of day 2 of the May 20-21, 2025 meeting of the Oncologic Drugs Advisory Committee to order. We'll start by going around the table and introducing ourselves by stating our names and affiliations. We'll start with the FDA to my left and go around the table.

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

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

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

DR. AGRAWAL: Sundeep Agrawal, Clinical Team Lead, Genitourinary Malignancies, FDA.

DR. HEISS: Brian Heiss, Medical Officer for Division of Oncology 1.

MS. JOHNSTON: Colette Johnston, patient representative.

DR. GRADISHAR: Bill Gradishar, breast oncologist, Northwestern.

DR. VASAN: Neil Vasan, breast oncologist, NYU Langone.

DR. SEO: Jessica Seo, Designated Federal Officer, FDA.

DR. SPRATT: Dan Spratt, Chair of Radiation Oncology at UH Seidman Cancer Center at Case Western Reserve University.

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

DR. MADAN: Ravi Madan, medical oncology, National Cancer Institute.

DR. McKEAN: Heidi McKean, community medical oncologist, Avera Cancer Institute.

DR. BALL: Mark Ball, urologist, National Cancer Institute.

DR. GARRAWAY: Isla Garraway, urologist, UCLA and the VA Greater Los Angeles Healthcare System.

DR. FRENKL: Tara Frenkl, Head of Global Medical and Evidence at Bayer Pharmaceuticals.

DR. SPRATT: Thank you.

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

In the spirit of the Federal Advisory Committee Act and the Government in their 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, the FDA will refrain from discussing details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you.

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

Conflict of Interest Statement

DR. SEO: Thank you, Dr. Spratt.

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

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

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those 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 their 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 discussion of new drug application, or NDA, 215793, for UGN-102, or mitomycin, intravesical solution, submitted by UroGen Pharma, Incorporated. The proposed indication, or use, is for the treatment of adult patients with low-grade intermediate-risk, non-muscle invasive bladder cancer. This is a particular matters meeting during which specific matters related to UroGen Pharma's NDA 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. Tara Frenkl is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Frenkl's role at this meeting is to represent industry in general and not any particular company. Dr. Frenkl is employed by Bayer Pharmaceuticals.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a

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

Thank you, and I'll return the floor to you, Dr. Spratt.

DR. SPRATT: Thank you.

We will now proceed with the FDA opening remarks, starting with Dr. Sundeep Agrawal.

FDA Opening Remarks - Sundeep Agrawal

DR. AGRAWAL: Good morning, everyone. My name is Sundeep Agrawal. I'm a hematologist and oncologist at the FDA's Center for Drug Evaluation and Research, Office of Oncologic Diseases. I'll be giving introductory comments regarding this application for the investigational product UGN-1O2, also known as mitomycin, which is being developed for the proposed indication of treatment of adult patients with recurrent low-grade

intermediate-risk, non-muscle invasive bladder cancer.

I will present background on UGN-102 and the purpose of the ODAC; the disease setting background regarding non-muscle invasive bladder cancer or NMIBC; relevant regulatory history data submitted by the applicant to support the new drug application or NDA; and finally, a summary and issues for committee discussion. I'll begin with a brief background on the drug and the summary of the purpose of today's ODAC.

The applicant's investigational product, UGN-102, is a formulation of mitomycin in an intravesical solution in a reverse thermal gel formulation. The drug is instilled once weekly for 6 weeks into the bladder via a urinary catheter. When infused, it's liquid, but it solidifies in the body to create a drug depot in the urinary bladder and dissolves over 6 hours. Treatment occurs in the outpatient setting.

The active drug mitomycin is an alkylating agent that inhibits the synthesis of DNA by

cross-inking of the DNA strand, which inhibits the DNA synthesis. Mitomycin was first FDA approved in 1974 as a systemic therapy to treat gastric and pancreatic carcinomas in combination with other chemotherapeutics. Off-label intravesical use in NMIBC is supported by reduction in recurrence risk as either a single post-operative installation after TURBT or as an adjuvant therapy after resection.

Mitomycin hydrogel is FDA approved to treat patients with low-grade upper tract urothelial carcinoma. It is the same active drug product as UGN-102 and is administered directly into the upper genitourinary tract.

The applicant's proposed indication is the treatment of adult patients with low-grade intermediate-risk NMIBC. This is a novel disease setting for drug development, as there are currently no FDA-approved drugs for this patient population. The applicant has used a single-arm trial design in the pivotal study to support their application.

FDA seeks input from the committee on the following.

Given uncertainty regarding interpretation of duration of response in low-grade intermediate-risk NMIBC, discuss whether randomized trials should be required in the future to assess the effectiveness of therapies in this disease setting, and is the overall benefit-risk of UGN-102 favorable for patients with recurrent low-grade intermediate-risk NMIBC.

Before reviewing data submitted by the applicant from these trials, I will discuss the disease setting background.

Bladder cancer can be considered broadly in three categories with implications for both treatment and prognosis: non-muscle invasive disease or NMIBC; muscle invasive bladder cancer or MIBC, and metastatic disease. Muscle invasive disease is defined by tumors that invade the muscle of the bladder. These patients are at risk of progression to metastatic disease and are generally treated with radical cystectomy, systemic

therapies, and/or radiation. Metastatic bladder cancer is considered incurable and is treated with systemic treatments with the aim to prolong survival or palliate symptoms of the disease.

NMIBC is on the earlier end of this disease spectrum. The figure here provides a visual representation of different tumors within the bladder wall that constitute non-muscle invasive disease. Carcinoma in situ, TA tumors, and T1 tumors do not invade the muscle.

The applicant's clinical trials enrolled patients with low-grade TA lesions. TA lesions are non-invasive papillary tumors. These may be high or low grade. Low-grade lesions have histology more similar to normal bladder tissue than high-grade tumors and are associated with less risk of recurrence or progression than high-grade tumors.

NMIBC is a heterogeneous disease state. The risks of non-muscle invasive bladder cancer are recurrence of disease after treatment or progression of disease. There is a wide range of

recurrence and progression probabilities. For example, based on a combined analysis of seven trials and over 2,000 patients with TA or T1 tumors, recurrence risk was estimated ranging from 15 to 61 percent at one year and 31 to 78 percent at five years, and progression risk was estimated at 1 to 17 percent at one year and 1 to 45 percent at five years.

These recurrence and progression estimates are based on cohorts with varying disease characteristics, patients who receive different prior treatments and older pathologic grading and staging systems, and it makes it difficult to quantify specific recurrence and progression rates for individual patients with NMIBC.

Several risk stratification models exist in most of these categories of low, intermediate, and high risk. Risk stratification is based on pathologic features such as tumor grade and stage and clinical features such as tumor size, multiple tumors, recurrence frequency, and time to recurrence. There is limited contemporary evidence

to correlate these categories with clinical outcomes, but the general categories are thought to broadly estimate likelihood of recurrence and progression.

This table is an example of risk stratification from the guidelines of the American Urologic Association. For intermediate-risk disease, there are five criteria that if any one is met would classify as intermediate-risk disease. The three criteria listed in the red box were used by the applicant to define intermediate-risk disease for their trials. For these patients, standard of care treatment typically involved transurethral resection of bladder tumor, or TURBT, with a single post-operative installation of intravesical chemotherapy.

Authors of several risk nomograms have noted that after high and low-risk categories were created, intermediate-risk disease was defined as NMIBC not fulfilling criteria for either high or low-risk categories. Because of the varying characteristics of these patients, heterogeneity

results, which makes the natural history of intermediate disease difficult to interpret, management can vary based on individual characteristics. TURBT alone may be used; or TURBT with an immediate single post-operative intravesical chemotherapy installation; or TURBT with immediate installation followed by maintenance therapies; and some patients may be candidates for active surveillance.

After initial treatment, surveillance for recurrence includes, first, cystoscopy and urine cytology approximately 3 to 4 months after initial TURBT, then these studies are conducted less frequently if negative. However, while several professional guidelines provide surveillance recommendations, there is some variation in clinical practice with respect to the surveillance procedures that are employed.

The diagram on the left of this slide demonstrates the TURBT procedure. A resectoscope is introduced through the urethra of the patient and tumor is resected upon visualization at

cystoscopy. On the right is a diagram of intravesical drug delivery, which is administered via a urinary catheter. The drug dwells in the bladder and patients urinate it out after the procedure.

The American College of Surgeons National Surgical Quality Improvement Program has collected adverse events associated with the TURBT procedure. They report an overall 30-day TURBT complication rate of approximately 5 to 8 percent. The most common complications include urinary tract infection and reoperations within 30 days, and serious complications include bladder perforation, infection, and hematuria.

The mortality rate has been estimated to be 0.8 percent. However, these data do not capture the risk of serious complications such as cardiac events and bladder perforation in a robust fashion, though it is reasonable to conclude that repeat TURBTs may predispose patients to increase cumulative risk of certain adverse events.

The applicant has submitted the following

rationale for the utility of UGN-102 in this population that may otherwise undergo TURBT. They note that TURBT procedures may not resect all tumor and the procedure itself could theoretically lead to tumor cell reimplantation after resection. They note a need for general anesthesia that exposes patients to safety risks, though the FDA review team notes that some patients may be candidates for more local approaches for this procedure, such as spinal anesthesia. They cite a high recurrence rate after TURBT and state that procedure limitations and post-operative complications suggest that a primary surgical approach is suboptimal.

I will now present a brief regulatory background on the development of UGN-102.

There have been multiple interactions between the applicant and the FDA dating back to 2016. The applicant has proposed several trial designs to evaluate UGN-102, including randomized non-inferiority designs evaluating a disease-free survival, or DFS endpoint; randomized superiority

designs with DFS; and single-arm trial designs using complete response and duration of response as endpoints. Throughout these interactions, FDA has recommended and encouraged a randomized trial design to assess the efficacy and safety of UGN-102 on several occasions.

In January of 2021, the applicant initiated the ATLAS trial, a randomized trial in patients with newly diagnosed or recurrent low-grade intermediate-risk and NMIBC. Patients were randomized to either UGN-102 with or without TURBT versus TURBT alone. The primary endpoint was disease-free survival, and key secondary endpoints included complete response rate, duration of response, and patient-reported outcomes.

Notably, the definition of DFS was different between arms, and patients in the TURBT alone arm did not receive a single post-operative installation of intravesical chemotherapy, which would be considered standard for many patients due to demonstrated ability to reduce recurrence with this addition. Thus, FDA and applicant did not

come to agreement on all aspects of this trial design prior to its initiation.

As this trial was ongoing, the applicant again proposed an additional single-arm trial in this population to support a future application. FDA stated that a single-arm design could possibly serve as a major trial to support approval if it enrolled a large number of patients, included sufficient duration of follow-up, and demonstrates sufficient efficacy and safety that encompasses outcomes with later TURBTs.

Additional FDA input noted that demonstrating treatment effect that is distinct from the natural history of disease would be critical, and the clinical meaningfulness would depend on the population enrolled, complete response and duration of response observed, and safety results. FDA also noted that this approach would likely require discussion at an advisory committee.

The applicant subsequently terminated the randomized ATLAS trial early and stated that the

reason was to pursue a single-arm study of UGN-102 that could support an approval, and further noted that this was a financial decision and not based on study findings. While terminated early, the FDA has evaluated data from ATLAS and has considered that it may be supportive. This will be discussed later in the presentation.

This is a schema for the ENVISION trial, the single-arm trial that the sponsor subsequently initiated to support their drug application for UGN-102. This is a single-arm trial in 223 evaluable patients with recurrent low-grade intermediate-risk NMIBC that recurred at least once after a prior TURBT.

UGN-102 was administered weekly for six consecutive weeks. Complete response rate at 3 months, which is a typical monitoring interval for NMIBC, was the primary endpoint. A key secondary endpoint was duration of response. In the follow-up period after the 3-month visit, patients underwent cystoscopy, urine cytology, and for-cause biopsies every 3 months.

Now, I want to briefly discuss challenges with the single-arm trial approach and why the FDA repeatedly recommended a randomized trial design to the applicant. Single-arm trials have supported FDA drug approvals when randomized trials are unethical or infeasible: for example, when there are suboptimal or no available therapies to randomize a control arm to; or in rare diseases or low frequency populations; or powering a randomized trial for an endpoint such as progression-free survival or overall survival is not possible.

However, single-arm trials have several limitations which include the potential for selection bias. A concurrent control provides context to evaluate observed results. Without a control, it is unclear whether results reported in a single-arm trial can be replicated and thus extrapolated to the indicated patient population and practice. This then often leads to a need to compare to historical control to provide context for efficacy, and a good historical control may not be available. A single-arm trial means there will

be a lack of comparative safety data.

Strengths of randomized trials are that these designs account for both known and unknown factors, which mitigates bias. A concurrent control provides context for efficacy and it allows for a robust comparative safety evaluation. Randomized trials should be used to support claims of efficacy unless truly infeasible or unethical. As we saw with the ATLAS trial, while FDA disagreed with some design elements of that trial, it did appear feasible to conduct a randomized trial in this population.

FDA acknowledges that complete response endpoints assessed in single-arm trials, supported by a prolonged duration of response, have supported drug approvals in the past. For example, we have the BCG unresponsive carcinoma in situ or CIS NMIBC paradigm. Standard of care historically had been radical cystectomy for these patients, and this is a morbid procedure with serious potential for mortality in some patients, as well as morbidity. Durable complete response to medical therapies

provides benefit by allowing the ability to delay or forego radical cystectomy.

Notably, at the time of these initial approvals, there was an unwillingness in the community to randomize to other medical therapies, which either had modest activity or were unavailable.

Mitomycin hydrogel is also approved for upper tract urothelial carcinoma based on durable complete response assessed in a single-arm trial, with the benefit also being avoiding a morbid procedure, radical nephroureterectomy. However, in this low-grade intermediate-risk NMIBC setting, the risks of TURBT appear to be a less than radical cystectomy and radical nephroureterectomy, and this affects the clinical meaningfulness of durable complete response in this population due to different benefit-risk considerations.

The risk to patients in this disease setting is primarily recurrence of disease; however, as I noted earlier, there is a wide range of recurrence outcomes in this population with poor historical

control. For example, some patients may never recur or may recur infrequently. For patients who do recur, they may require additional TURBT procedures, which differ in risks of morbidity and mortality compared to more radical procedures such as radical cystectomy and radical nephroureterectomy.

The lack of concurrent control presents challenges -- for example, the potential for selection bias -- and is unclear if duration of response reported is due to the drug or the natural history of the disease. Comparative safety data is not possible to obtain in the single-arm ENVISION trial and is only available from the randomized ATLAS trial, though these data are limited and will be discussed further by my colleague, Dr. Heiss.

So, it will be helpful to get the committee's input, given uncertainty regarding interpretation of duration of response in low-grade intermediate-risk NMIBC, should randomized trials be required in the future to assess the effectiveness of therapies in this disease setting.

Now, I will present data submitted by the applicant to support this NDA, and then we will revisit this disease background I just presented in the context of that data.

In the ENVISION trial, out of 223 evaluable patients, 77.6 percent had a complete response at 3 months. As for reasons patients did not have a CR, residual disease was the most common. Progression events were rare. Seventy-nine percent of patients who achieved a complete response at 3 months were still in complete response one year later.

The FDA review team selected patients in the randomized ATLAS trial who met eligibility criteria for ENVISION, the single-arm trial. These were patients with only recurrent low-grade intermediate-risk NMIBC. Fifty-one patients in the UGN arm met these criteria. The CR rate was 72.5 percent in this exploratory analysis from ATLAS, which was consistent with that of ENVISION. This was reassuring. FDA is not presenting the duration of response data here from ATLAS given

differences in follow-up durations between trials. I will also note that cross-trial comparisons such as this may result in bias; thus, these findings should be interpreted with caution.

In evaluating safety, the most common adverse events were genitourinary toxicities, for example, urinary tract infection, dysuria, and hematuria. Most events were low grade and resolved during or after the treatment course with UGN-102. The randomized ATLAS trial provided some comparative safety data; however, interpretation is limited due to differences in timings of assessment between arms.

Exploratory safety findings from ATLAS demonstrate UGN-102 had higher rates of adverse events, including grade 3 or 4 events, and higher rates of genitourinary toxicities such as dysuria, frequent urination, and erectile dysfunction. In ATLAS, there did not appear to be any serious events associated with having to undergo general anesthesia, though, again, these data are challenging to interpret due to differences in

safety assessments between arms and due to limited follow-up. My colleague, Dr. Heiss, will discuss safety in more detail.

Now, I would like to provide a summary and discuss the issues for committee discussion.

The current standard of care for patients with recurrent low-grade intermediate-risk NMIBC is TURBT with a post-operative installation of chemotherapy after the procedure. Some of these patients may be candidates for active surveillance depending on their individual risk because the risks of disease-related morbidity or progression to more advanced disease may be rare.

Patients who have frequent recurrences may potentially need to undergo multiple sequential TURBT procedures, which can predispose patients to risks associated with general anesthesia and adverse events such as infection, hematuria, or bladder perforation.

UGN-102 may provide a non-operative treatment option and appears to have activity since obtaining a complete response without intervention

is not expected. Durability of response is a key component of the efficacy evaluation. A complete response of short duration is unlikely to be clinically meaningful, as patients would be at risk of developing toxicity throughout and after the 6-week UGN-102 treatment course and may recur shortly thereafter, requiring additional intervention.

A complete response that is supported by a prolonged duration of response may be clinically meaningful, as this may obviate the need for at least one subsequent TURBT procedure; however, the duration of response of UGN-102 is difficult to interpret. While the single-arm trial design of ENVISION and supportive data from ATLAS do demonstrate the drug activity of UGN-102 via the reported CR rate, the single-arm design does not allow adequate assessment of duration of response, as this is a time-to-event endpoint.

It is unclear whether the duration of response observed is due to the drug effect or the natural history of the disease. The low-grade

intermediate-risk NMIBC population is a heterogeneous one with respect to recurrence and progression outcomes, so it is difficult to predict which patients may recur more often and require additional interventions versus those who recur infrequently or not at all. And the challenge in interpreting durability data is further complicated by lack of good historical control on the recurrence-free interval due to these wide recurrence probabilities reported in the available literature. It is unclear whether current risk stratification models are sufficient to identify a homogeneous population with respect to oncologic outcomes in these patients.

In evaluating the overall benefit-risk assessment, it appears UGN-102 can induce complete responses in this patient population; however, the duration of response is challenging to interpret. We should consider the acute genitourinary toxicity with UGN-102 treatment that results from weekly catheterization and treatment for 6 weeks, with toxicity in some patients taking additional time

after the 6th dose to resolve. There is a lack of randomized data to contextualize safety, which results in an inability to understand the risks of UGN-102 in the context of available standard of care.

So, is a single-arm trial sufficient to inform benefit-risk in this setting? There are several weeks of potential toxicity burden, an unclear recurrence risk for individual patients with low-grade intermediate-risk NMIBC, and uncertainty as to whether the duration of response observed in ENVISION can be attributed to the drug or the disease.

Lastly, the benefit-risk considerations differ in a low-grade intermediate-risk population compared to other settings where single-arm trials have supported drug approvals such as BCG unresponsive CIS or upper tract urothelial carcinoma. Patients with low-grade intermediate-risk NMIBC may require additional TURBTs, whereas patients in the aforementioned examples are at risk of morbidity and mortality

from radical procedures such as cystectomy and radical nephroureterectomy.

The issue we ask the committee to discuss is, given uncertainty regarding interpretation of duration of response in low-grade intermediate-risk NMIBC, discuss whether randomized trials should be required in the future to assess the effectiveness of therapies in this disease setting.

The voting question is as follows. Is the overall benefit-risk of UGN-102 favorable for patients with recurrent low-grade intermediate-risk NMIBC? Thank you.

DR. SPRATT: Thank you, Dr. Agrawal.

Both the 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 participants, including the industry's non-employee presenters, to advise the committee of any

financial relationships that they may have with industry, such as consulting fees, travel expenses, honoraria, and interest in a sponsor, including equity interests and those based upon the outcome of this 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 the issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the presentations from UroGen Pharma, Incorporated.

Applicant Presentation - Mark Schoenberg

DR. SCHOENBERG: Great. Thank you.

Good morning. My name is Mark Schoenberg. I'm the Chief Medical Officer of UroGen Pharma. I'm also a practicing urologist, and I've spent the last 25 years in my career caring for patients with bladder cancer. We would like to thank the FDA and the advisory committee for the privilege of

presenting data supporting UGN-102 for the treatment of non-muscle invasive bladder cancer or NMIBC.

UGN-102 was developed as a primary office-based medical alternative to a surgical procedure called transurethral resection of bladder tumor, or TURBT, for patients diagnosed with a common form of NMIBC called low-grade intermediate-risk disease. Like most bladder cancers in the U.S., intermediate-risk disease typically occurs in elderly Caucasian men who often have multiple comorbidities.

This form of bladder cancer has a high likelihood of recurrence but a low likelihood of disease progression. If approved, UGN-102 would offer these patients their first and only primary non-surgical option for treatment, one that provides a long duration of response and lessens the burden of repeated TURBTs.

UGN-102 combines mitomycin with a reverse thermal gel. It's instilled into the bladder as a chilled liquid where it converts to a solid gel at

body temperature. The gel acts as a drug depot and achieves a dwell time of about 6 hours, which is 3 to 6 times longer than can be achieved with aqueous medications. The sustained release leads to local chemoablation of tumors, but systemic exposure is low, and this minimizes systemic toxicity. UGN-102 can be administered by a nurse in an office.

UGN-102 is actually UroGen's second medicine to employ the same platform technology and active drug. Jelmyto was approved in 2020 as a breakthrough therapy for upper tract urothelial carcinoma, a related disease affecting the interior of the kidney and the ureter. Jelmyto was approved on the basis of a single-arm trial. It produces a median duration of response of about 4 years, and its approval has transformed the management paradigm for patients with upper tract disease.

The proposed indication for UGN-102 is the treatment of adult patients with recurrent low-grade intermediate-risk non-muscle invasive bladder cancer; and while our clinical studies

support a benefit in patients with newly diagnosed or recurrent disease, the FDA requested that our pivotal study focus on patients with recurrent disease because they have the highest unmet medical need.

We conducted four late-phase clinical trials, three of which will be presented today. The ENVISION trial, the pivotal trial, was performed in patients with recurrent disease. The OPTIMA II AND ATLAS trials provide supportive evidence of efficacy and safety.

It's important to understand how this program evolved over the past few years, prompted by extensive conversations with the FDA about the best way to demonstrate the clinical value of UGN-102.

Based on discussions with the FDA, we initiated ATLAS in January of 2021 as a randomized study comparing UGN-102 to TURBT; however, the FDA required that we demonstrate superiority to TURBT, a surgical procedure, rather than non-inferiority. This appeared to be an unprecedented regulatory

hurdle, and we never fully aligned on key elements of the study design. And for these reasons, we continue to explore alternative development pathways, including a single-arm trial.

When the FDA agreed that a single-arm ENVISION trial could be the basis for approval and without knowledge of the ATLAS data, we halted enrollment in ATLAS in November of 2021. At that point, ATLAS was 40 percent enrolled, so we continued to follow patients to collect valuable supportive efficacy and safety data. We opened ENVISION as our pivotal trial in February of 2022, and we submitted the NDA in August of 2024 through the 505(b)(2) pathway.

Today, we will show you that the duration of response data from a single-arm trial can establish the efficacy of UGN-102. ENVISION is a large trial with adequate follow-up. The patient population we studied accurately reflects the target population for the medicine. The results demonstrate clinically meaningful complete response and duration of response, and the study met all

criteria set forth by the FDA to support approval of UGN-102. These results can be reliably compared to results obtained following TURBT, and patients benefit from treatment with UGN-102, which decreases reliance on TURBT with its associated risks.

In addition, ATLAS provides strong support of evidence of efficacy and durability in patients with recurrent disease. The safety profile of UGN-102 is acceptable and manageable in standard urologic practice, and the totality of the data from our studies, which enrolled almost 600 patients, demonstrates a favorable benefit-risk profile. If approved, UGN-102 would provide patients with a treatment option that can break the cycle of repeated TURBTs.

Here's the agenda for the remainder of our presentation. First, Dr. Sam Chang of Vanderbilt University, Department of Urology, will discuss the unmet medical need; then Dr. Michael Louie will present advocacy data; and Dr. Sunil Raju will present the safety data supporting the application.

And then finally, Dr. Max Kates of the Brady Urologic Institute of the Johns Hopkins University will present his perspective on the clinical use of UGN-102.

And now I'll invite Dr. Chang to the podium.

Applicant Presentation - Sam Chang

DR. CHANG: Thank you, Dr. Schoenberg.

I'm a little height challenged, so I'm going to utilize the stool and, unfortunately, you might be able to see me now. My name is Sam Chang. I'm a urologic surgeon at Vanderbilt and lead their Division of Urologic Oncology. I also chair the American Urologic Association guidelines on bladder cancer.

Today, I'm going to discuss and describe the important need for patients to break the cycle of repeated TURBTs with intermediate-risk bladder cancer. I'm a paid advisor and consultant from different companies, including UroGen, but I have no financial interest in the outcome of this meeting.

Bladder cancers are common in the U.S.

Median age is 73. Each year, more than 80,000 cases are diagnosed, and 75 percent of these are non-muscle invasive disease. Fortunately, the prognosis for non-muscle invasive disease is good, and it's estimated that more than 700,000 Americans live with bladder cancer today. The prevalence of recurrent immediate-risk NMIBC is estimated at approximately 60,000.

Treatment of bladder cancer depends on risk stratification that, in part, depends on pathologic stage and grade. TA and T1 tumors are non-muscle invasive disease and TA tumors are confined to the urothelium. T1 tumors involve the laminar propia. Grade depends on microscopic features and is designated usually as high grade or low grade, with the majority of bladder cancers, in fact, being low grade.

Intermediate-risk NMIBC includes low-grade TA tumors that are large, greater than 3 centimeters, multifocal, and are recurrent, as well as low-grade T1 tumors. Although these patients have a high chance of recurrence, they

have a minimal chance of disease progression. And if we focus on TA non-invasive disease, these are in fact the most common presenting cancers in clinical practice.

NMIBC is, in fact, one of the most recurrent of all cancers. Within a 5-year time period, 68 percent of patients will have two or more recurrences, and in fact almost a quarter of these patients will have five or more recurrences. This high rate of recurrence has been seen in multiple studies.

Tumor status at 3 months -- that's evaluation after an initial TURBT -- is the strongest predictor of future recurrence; therefore, a 3-month complete response rate is clinically meaningful. An example is a study by Mariappan and Smith. Among patients who were free of disease at 3 months, the risk of recurrence at one year was 18 percent. But if you had disease at that 3-month mark, that risk of recurrence was almost 60 percent. All of our guidelines, in fact, recommend follow-up cystoscopy at 3 months to help

detect residual or recurrent disease.

Standard of care treatment for these patients is TURBT performed usually in the operating room and under general anesthesia. This process involves a preoperative evaluation, anesthetic clearance, a day that usually is a full day at the surgery center, and then several days to recover at home.

The rigid resectoscope is inserted into the bladder and is used to cut through these papillary tumors with electrocautery. You can see here what a typical procedure looks like to a surgeon. It's informative diagnostically, provides a visual impression of the extended disease, and provides a pathologic specimen, but it's an imperfect therapeutic intervention, especially when we consider the high recurrence rate.

There are limitations of what we do. The surgeons can only remove what they can see, and we many times cannot see the full extent of multifocal disease. And at times, normal appearing urothelium can, in fact, hide malignant transformation.

Surgery does not reliably address all disease and, consequently, residual tumors are found 30 to 45 percent of the time within weeks after a TURBT.

Importantly to consider is most patients with bladder cancer are older, have multiple comorbidities, so putting them through repeated TURBTs. And the risk of that procedure is real, and, also, you have to consider the general anesthetic risks. Partly because these patients require continued active surveillance and repeated TURBTs, bladder cancer has been described as one of the most costly of all cancers.

TURBT has a predictable set of post-operative risks, like hematuria, like bladder pain, like frequency, and can result in serious complications like perforation of the bladder, particularly with repeated procedures. A substantial number of patients will have an adverse event within 90 days of a TURBT, and TURBT is the outpatient urologic procedure that is most likely to result in an unexpected post-operative hospitalization. It's not a trivial surgery. In

fact, it carries almost a 1 percent chance of death. In addition, general anesthesia can be associated with cardiopulmonary complications, as well as an impact on cognitive decline, particularly in these older patients with non-muscle invasive bladder cancer.

The AUA guidelines discuss the use of intravesical therapy. To be clear, the guidelines do not recommend its use. The guidelines say a treatment after TURBT should be considered. This, in part, is due to limited effectiveness of this treatment, especially in patients with recurrent and multifocal disease like those enrolled in ENVISION and ATLAS. For this and many other reasons, peri-operative usage is limited in the U.S. A large retrospective study showed that only 18 percent of U.S. practices actually use intravesical chemotherapy post-TURBT.

Let's look at a typical patient journey. Why do I think we need another treatment option, and why do I think patients need another treatment option? Here's a patient diagnosed with a

low-grade intermediate-risk non-muscle invasive bladder cancer. This patient undergoes TURBT followed by surveillance. About half of the patients with intermediate-risk disease will require another TURBT within a short period of time, and many will have multiple recurrences and require multiple TURBTs. They can have significant hematuria. They may require and many do go home with a urinary catheter. Patients need another option, another non-surgical option that can break the cycle of repeated TURBTs and provide a longer duration of response. Currently, there is no approved pharmacotherapy that obviates the need of a TURBT, and chemo ablates tumors.

So to summarize, low-grade intermediate-risk disease recurs frequently and is inadequately controlled with TURBT. Each time we do a resection, the patient has a potential for complications. And we know that TURBT has substantial costs, not only to the patient but to the patient's family, not only in terms of financial costs but social costs. We need a more

scientifically-based approach that treats the entire bladder effectively and for a longer period of time. I think patients want and patients need another choice.

Now, I'll turn over to Dr. Louie.

Applicant Presentation - Michael Louie

DR. LOUIE: Thank you, Dr. Chang.

My name is Mike Louie, and I'm an Executive Vice President of Clinical Development and Medical Affairs at UroGen. I'll be presenting the late-phase development program, as well as the UGN-102 efficacy data.

The efficacy of UGN-102 was assessed in three late-phase trials through measurement of two key endpoints, complete response rate and duration of response. Because bladder tumors don't spontaneously regress, these endpoints directly reflect the anti-tumor effect of UGN-102. The study population across all three trials consisted of patients with low-grade intermediate-risk non-muscle invasive bladder cancer, and all patients received the target dose of 75 milligrams

instilled via urinary catheter once weekly for 6 weeks.

ENVISION, the pivotal phase 3 trial, enrolled 240 patients with recurrent intermediate-risk disease. The primary endpoint is complete response evaluated at 3 months with cystoscopy, for-cause biopsy, and urine cytology. The key secondary endpoint is duration of response defined as a time from 3 month at complete response to recurrence, progression, or death, and estimated by Kaplan-Meier method. ENVISION is an ongoing trial, and a minimum follow-up of 18 months after 3-month complete response was included in the NDA.

OPTIMA II was a phase 2b proof-of-concept study that enrolled 63 patients with recurrent or newly diagnosed disease. Like ENVISION, the primary endpoint was complete response rate measured at 3 months, and the secondary endpoint was duration of response. In OPTIMA II, patients were followed for 9 months after 3-month complete response.

ATLAS was a supportive phase 3 randomized

controlled trial that enrolled 282 patients with a recurrent or newly diagnosed disease. Unlike the other two trials, the primary endpoint was disease-free survival; however, the secondary endpoints did include complete response rate measured at 3 months and duration of response. In ATLAS, patients were followed for a minimum of 12 months after 3-month complete response.

Quality of life assessments were completed by participants in all three trials, and the data are described in the briefing document. Per agreement with the agency, efficacy analyses are being presented for the FDA analysis population, which consists of patients from the development program with recurrent intermediate-risk disease. Furthermore, today's efficacy discussion will focus on results from the two phase 3 trials, ENVISION and ATLAS.

The pivotal ENVISION trial enrolled 240 patients at 56 sites in 10 countries. Investigators were instructed to document that residual tumor was present after they performed the

diagnostic biopsy and before giving treatment with UGN-102. We, therefore, know that tumor was present in all patients prior to receiving treatment with UGN-102.

At baseline, patients initiated the six once-weekly installations with UGN-102. The primary endpoint, complete response rate, was determined at 3 months. Patients in complete response entered the follow-up period, which extends through 63 months. During follow-up, patients are regularly assessed for recurrence or progression. Patients not in complete response received investigator designated standard of care, which was primarily TURBT, and then entered the follow-up period. At first recurrence during follow-up or disease progression at any time, patients received standard of care followed by an end-of-study visit.

ENVISION was designed to serve as the basis for approval of UGN-102. Certain criteria were agreed upon with the agency that would support approval of UGN-102, and ENVISION met all of these

criteria. The study population consists of patients with a history of low-grade non-muscle invasive bladder cancer requiring TURBT. The current standard of care, TURBT, has failed in these patients, and, therefore, they have the greatest unmet need for an alternative treatment option.

ENVISION is characterized by significant enrollment. In fact, it's the largest registrational trial ever conducted in patients with low-grade intermediate-risk disease. ENVISION includes extended follow-up. Duration of response to UGN-102 will continue to be assessed for up to 5 years. Finally, we assessed the outcomes of TURBTs that were performed after patients were treated with UGN-102, and we found no increase in the rate of complications following these TURBTs.

The key inclusion and exclusion criteria for ENVISION also apply to ATLAS and OPTIMA II. The exception is that ENVISION required a history of low-grade non-muscle invasive bladder cancer, whereas the other two trials enrolled patients with

both recurrent and newly diagnosed intermediate-risk disease. All patients in the development program had low-grade TA or papillary disease. This is the most common presentation of intermediate-risk disease.

Intermediate risk was defined as having one or two of the following criteria: multiple tumors, a solitary tumor with a diameter of greater than 3 centimeters, or early or frequent recurrence. Exclusion criteria are shown on the right and are described in the briefing document. Of note, patients with overactive bladder were not excluded from the UGN-102 development program. These patients often don't qualify for trials in non-muscle invasive bladder cancer, as they have difficulty retaining aqueous intravesical therapy; however, this is not an issue with the reverse thermal gel formulation of UGN-102.

The baseline demographics and tumor prognostic factors in the FDA analysis population of ENVISION and across the rest of the development program were consistent with those of patients with

recurrent intermediate-risk disease in the United States. Patients had a median age of 70 and were primarily male. Over 50 percent had had an episode of low-grade disease within one year of the current diagnosis, and close to 40 percent had a history of two or more prior NMIBC episodes.

Patients generally presented with multiple small tumors at baseline, consistent with the typical presentation of patients with recurrent intermediate-risk disease. Greater than 80 percent of these patients had multiple tumors and a tumor burden of less than or equal to 3 centimeters. Greater than 90 percent had a longest tumor diameter of less than or equal to 3 centimeters.

The EORTC risk score predicts the risk of recurrence in patients with non-muscle invasive bladder cancer. It's calculated using multiple tumor prognostic factors, including those shown on this slide. Close to 90 percent of patients in ENVISION had an EORTC risk score of 5 to 11. The likelihood that these patients would experience a recurrence within the next year is between 40 and

50 percent.

Importantly, per the investigators, almost all patients would have undergone a TURBT for their index lesions if they had not participated in the trial; that is to say, ENVISION participants were not candidates for active surveillance or fulguration.

Treatment with UGN-102 was associated with a robust complete response rate at 3 months of 77.6 percent. The 95 percent confidence interval was narrow, indicating that this measurement was precise. About 22 percent of patients were not in complete response at 3 months, mostly due to the presence of residual low-grade disease. The low rate of progression is consistent with that reported in the literature for intermediate-risk disease, and there were minimal missing data.

The complete response rate achieved with UGN-102 was consistent regardless of the baseline demographics or the tumor prognostic factors. The forest plot is depicting the ratio of complete response rates for each pair of subgroups. The

point estimates for the CRR ratios all hover around 1 with overlapping 95 percent confidence intervals, indicating that response to UGN-102 was similar across all prespecified subgroups.

Not only was the complete response rate achieved with UGN-102 robust, it was also highly durable. At a median follow-up of 19 months after 3-month complete response, the median duration of response was not estimable due to the low number of events. The probability of remaining event free 12 months after 3-month complete response was 83.3 percent, and it was 81.2 percent at 18 months after 3-month complete response. The duration of response estimates have narrow confidence intervals, indicating there was limited variability in patients' response to UGN-102 over time.

FDA's analysis resulted in a much lower measurement of duration of response at 18 months. For protocol, there was a 2-week window around the 18-month visit during which patients could be assessed for response. Twenty-eight patients were assessed for response just prior to month 18. Ten

of these patients had their assessment one day prior to month 18. All of these patients were found to be in complete response and censored at the time of their last follow-up. However, because these patients were not assessed exactly at 18 months, the FDA reclassified these patients as treatment failures, which is not consistent with the clinical data, giving result that significantly underestimates the true duration of response at 18 months. Importantly, 27 of these 28 patients in question remain in the trial and are presumably still in complete response.

Participants in ENVISION all had a history of being treated with TURBT and were, therefore, able to directly compare their experiences with UGN-102 versus with TURBT. Structured interviews of U.S. participants were conducted at baseline and month 3 by independent investigators at the University of North Carolina, and the results were published in the Journal of Urology.

The investigators reported that over 90 percent of patients would recommend UGN-102 over

TURBT. Reasons included less impact on activities of daily living, including work, recreation, exercise, and sexual activity, as well as less bleeding and fewer issues related to the placement of urinary catheters. Overall, the investigators found that patients perceived UGN-102 to be less painful, less invasive, and less time consuming compared to TURBT. Additionally, patient-reported outcome data collected across the development program showed that UGN-102 did not adversely affect patient's physical functioning or their symptom burden.

The supportive phase 3 ATLAS trial randomized 282 patients with recurrent or newly diagnosed disease in a 1 to 1 fashion to receive either UGN-102 or TURBT at baseline. Response to treatment was evaluated at 3 months. Patients in complete response entered the follow-up period and were monitored for recurrence or progression. Patients not in complete response due to residual low-grade disease underwent a TURBT and then entered follow-up.

Enrollment in ATLAS was halted without knowledge of the data once a decision was made to initiate ENVISION. UroGen remained blinded to the data until all patients had completed at least 15 months of follow-up.

The endpoints, complete response rate and duration of response, reflect the impact of the baseline interventions only; that is UGN-102 alone versus TURBT. These endpoints are not affected by TURBTs that were done at 3 months for non-complete responders; so we're focusing the ATLAS efficacy discussion on complete response rate and duration of response.

Since these were the primary and secondary endpoints in ENVISION and OPTIMA II, this helped us assess the consistency of UGN-102's impact on patients with recurrent disease across the development program. Results for the primary endpoint, disease-free survival, are discussed in the briefing document.

UGN-102 alone resulted in a higher complete response rate at 3 months than TURBT. The response

rates were 72.5 percent with UGN-102 alone versus 56.1 percent with TURBT. What this means for patients is that chemoablation with UGN-102 achieved better disease eradication than TURBT without the need for an invasive procedure under general anesthesia.

Not only was the complete response rate with UGN-102 higher than with TURBT, the duration of response was also longer with UGN-102. At a median follow-up of 12 months after 3-month complete response, the median duration of response was not estimable in the UGN-102 arm compared with 9.1 months in the TURBT arm. Twelve months after 3-month complete response, the probability of remaining event free was 65.2 percent with UGN-102 versus 41.9 percent with TURBT.

We found that chemoablation with UGN-102 reduced the need for TURBTs under general anesthesia in this highly recurrent population. In ATLAS, avoidance of surgery was a prespecified endpoint. Shown here is the total number of TURBTs performed over the duration of the trial. In dark

gray are the TURBTs that were done at baseline per protocol. In light gray are TURBTs that were done during the follow-up for recurrence or progression. Over the duration of the trial, there were 22 TURBTs done in the UGN-102 arm compared with 85 in the TURBT arm.

We also looked at this in an exposure adjusted manner, which showed that there were 0.4 TURBTs per patient-year in the UGN-102 arm compared with 1.8 per patient-year in the TURBT arm. Reduction in the number of TURBTs under general anesthesia is clinically meaningful to this elderly comorbid population.

The complete response rate and duration of response achieved with UGN-102 were remarkably consistent across the development program and compare favorably to standard of care. Complete response rate is on the left and duration of response 12 months after 3-month complete response rate is on the right in the FDA analysis populations of each study. We can see that the results are consistent, with more precision being

provided in ENVISION due to its larger sample size.

To put UGN-102 efficacy data into clinical context relative to standard of care, the best comparator is the TURBT arm of ATLAS. The study procedures and the baseline characteristics were essentially the same as for patients who received UGN-102. The point estimates for complete response rate and 12-month duration of response achieved with TURBT are lower than those achieved with UGN-102. Note that there's no overlap in the 95 percent confidence intervals for the two endpoints between the TURBT arm of ATLAS and ENVISION.

For further context, we looked at a contemporary trial reported by Pedersen et al., also conducted in patients with recurrent intermediate-risk disease. In this study, patients were treated with TURBT, and 25 percent of them received a single post-op dose of intravesical mitomycin; therefore, this population received typical care for intermediate-risk disease.

The complete response rate in the Pedersen

study is similar to that of the TURBT arm of ATLAS, around 50 percent. Recently, the 12-month recurrence-free survival from the Pedersen cohort was reported as 44.1 percent. Looking at the right side of the slide, this result is similar to the 12-month duration of response in the ATLAS TURBT arm, 41.9 percent.

We did an exploratory analysis of the probability of recurrence in patients from ENVISION who had an EORTC risk score of 5 to 11, which was about 90 percent of the study population. Following treatment with UGN-102, the probability of having a recurrence at 2 years was 37 percent. To put this into context and acknowledging the limitations of cross-trial comparisons, Sylvester and colleagues conducted a meta-analysis in patients with intermediate-risk disease and an EORTC risk score of 5 to 11 who were treated with TURBT with or without a single installation of intravesical therapy. The probability of having a recurrence 2 years after treatment was about 55 percent.

In summary, the totality of the data indicate that UGN-102 is a highly efficacious treatment for patients with recurrent low-grade intermediate-risk non-muscle invasive bladder cancer. The pivotal ENVISION trial demonstrated robust and clinically meaningful efficacy. The randomized ATLAS trial demonstrated that UGN-102 was associated with a higher complete response rate and a longer duration of response in TURBT.

Also, UGN-102 reduced the need for TURBT, which is associated with a mortality rate of close to 1 percent in which patients with intermediate-risk disease typically experience multiple times during their lifetime. Ninety percent of patients interviewed would recommend UGN-102 over TURBT, and patient-reported outcomes showed that quality of life was not adversely impacted by UGN-102. Finally, UGN-102 efficacy results were consistent across the late-phase trials in the FDA analysis population of 329 patients, and UGN-102's efficacy compares favorably to that of standard of care with TURBT

with or without intravesical chemotherapy.

Thank you, and now Dr. Sunil Raju will discuss the safety profile of UGN-102.

Applicant Presentation - Sunil Raju

DR. RAJU: Thank you, Dr. Louie.

My name is Sunil Raju, Vice President in Clinical Development at UroGen Pharma. I'll be presenting the safety summary of the UGN-102 development program. Before describing the safety profile of UGN-102, I'd like to first highlight a few important details regarding pharmacokinetics.

Following local administration of UGN-102 into the bladder, there's minimal systemic absorption of mitomycin. The mean Cmax of the target dose of 75 milligrams was 2.3 nanograms per mL, which is less than 1 percent of the expected Cmax after intravenous administration of mitomycin and less than 1 percent of the mitomycin plasma concentration associated with myelosuppression.

We'll start with an integrated summary of safety across pool 2, which includes the four late-phase studies. Pool 2 is a robust safety data

set comprising 449 patients who received any treatment with UGN-102. If we look at exposure by the number of UGN-102 installations received, the vast majority of patients, 94 percent, received all six of their planned installations and over 97 percent received five or more installations.

Here's the overall summary of adverse events associated with UGN-102 in pool 2. I'll present the results by three time periods: the overall time period, the period up to 3 months, and post-3 months.

If we focus on the overall time period, adverse events were reported in 68 percent of patients. Thirty-nine percent had events considered treatment related and 29 percent had procedure-related events, which are those related to catheter insertion, cystoscopy, or biopsy. There's a low rate of AEs leading to treatment or study discontinuation. Grade 3 or higher AEs were reported in 11.6 percent of patients and SAEs were reported in 10.9 percent of patients. Very few of these SAEs were considered treatment or procedure

related.

Two patients had treatment-related SAEs of urethral stenosis and urinary retention. Four deaths occurred in UGN-102-treated patients, and all of these were assessed as unrelated study treatment or procedure. They were due to cardiac failure, cardiac disorder, pneumonia, and death due to an unknown cause. Adverse events of special interest occurred in about 50 percent of patients and were mostly low grade in severity. There was no clinically meaningful risk of bone marrow suppression.

When we look at the period up to 3 months, you'll see that the majority of AEs occurred in this time period. The incidence of grade 3 or higher AEs and SAEs were similar in the period up to 3 months and post-3 months. In general, the incidence of treatment-related or procedure-related SAEs was low, and the majority occurred in the period up to 3 months.

Here are the most frequently reported AEs occurring in greater than 5 percent of patients in

pool 2. The majority of these events were low grade, and with the exception of fatigue, were localized to the lower urinary tract. And among patients with an AESI of lower urinary tract symptoms, the median time to onset was 17 days. These tended to be limited with a median duration of 8 days for the first event. The incidences of these lower urinary tract symptoms were highest at weeks 4 and 5 at approximately 13 percent, and then dropped to 2 percent shortly after week 6.

AEs within the system organ class of renal and urinary disorders were the most frequently reported, and the incidence of grade 3 or higher AEs was low at 2.2 percent, and for SAEs, the incidence was similarly low.

When we look at the overall summary of adverse events in the pivotal trial ENVISION, the safety profile of UGN-102 is similar to what we observed in the integrated pool 2 analysis. The majority of events occurred in the first 3 months. The incidence rates of grade 3 or higher AEs and SAEs were comparable to the integrated analysis,

and there was a low incidence of treatment- or procedure-related SAEs.

In summary, adverse events associated with UGN-102 were mostly localized to the urinary tract. They were low grade in severity, reversible, and occurred in the first 3 months. In addition, patients did not perceive UGN-102 to adversely affect their quality of life or symptom burden.

Within the renal and urinary disorder system organ class, where AEs will most commonly occur, the frequency of grade 3 or higher AEs and SAEs was low. And finally, treatment with UGN-102 results in minimal systemic absorption of mitomycin with a low risk of systemic side effects, and there's no clinically meaningful risk of bone marrow suppression. Overall, the safety profile of UGN-102 is acceptable and manageable as part of standard urological practice.

Thank you, and I'll now turn the podium over to Dr. Kates.

Applicant Presentation - Max Kates

DR. KATES: Thank you, Dr. Raju.

My name is Max Kates. I'm an Associate Professor of Urology and Director of Urological Oncology at Johns Hopkins Hospital. And it's really a privilege to speak to you all today to share my perspective on what UGN-102 brings to the table and, really, how I would use it in my practice. I'm a paid consultant to UroGen, but I have no financial interest in the outcome of this meeting.

As a clinician, when considering the unmet clinical need, I really think about my patients. This is a 72-year-old gentleman whose intermediate-risk NMIBC was treated in the community, and he subsequently was referred to me in 2024. He was first diagnosed with low-grade non-invasive papillary bladder cancer in March of 2023, and then over the next year, he underwent three TURBTs for disease recurrences. After he was referred to me, he presented yet again in August of 2024 with gross hematuria, passing large blood clots, and now four new papillary tumors.

So, in this situation, clearly another TURBT

was not going to be effective. Moreover, I worry about the long-term risks of repeated anesthesia to cognition and repeated bladder wall resection and scarring to his urinary symptoms over time. This is the type of patient that urologists see all the time, where TURBT is ineffective and repeated resections are harmful. And right now, there is no option other than another TURBT for this type of patient; so we need UGN-102 as an alternative to the repetitive cycle of surgery.

So in that context, I view UGN-102 as a crucial tool to break this cycle of TURBTs in my patients who are destined to recur otherwise. It provides a medical option for patients and urologists.

In the ENVISION study, UGN-102 produced durable responses in 78 percent of patients, and those responses were durable in over 80 percent of patients for at least 18 months after achieving a CR. This is not the natural history of disease in this patient population, based both on my experience and the literature. The clear benefits

outlined in the ENVISION trial would be impressive to any urologist because this is an ablative agent given without resecting the tumor. In addition, the PRO data shows that patients really want choices.

So if we consider all patients enrolled per the FDA analysis, based on the data from ENVISION, what I can tell my patients is that with UGN-102, they have a 70 percent chance of avoiding a TURBT in the first year and a 63 percent chance of avoiding a TURBT within 2 years. This means that, at worst, in nearly two-thirds of my patients, a TURBT could be delayed for at least 2 years, and in some of my patients, TURBT is going to be avoided altogether. The risks are the expected toxicities of intravesical chemotherapy, which include lower urinary tract symptoms, which are mostly low-grade and, frankly, the urologists are accustomed to managing every day in our clinic.

In addition to the obvious clinical benefits, UGN-102 is also much easier on patients. UGN-102 is administered in the urology office by a

nurse or advanced practice provider, whereas TURBT is done in the hospital or surgery center. UGN-102 takes less than an hour in the office, whereas TURBT is 4 to 6 hours when you include the pre-op, the intra-op, the post-op recovery, and patients need a friend or family member to drive them home afterwards.

UGN-102, probably most importantly, doesn't require general anesthesia. It's administered through a catheter with lidocaine gel, whereas TURBT is done under general anesthesia, which of course requires preoperative clearance by a primary care doctor, and in this patient population, often by a cardiologist or a pulmonologist.

And finally, patients treated with UGN-102 can resume normal daily activities, whether it's work or something else, immediately afterwards, whereas TURBT requires at least 2 to 3 days of recovery away from those activities, sometimes with a post-surgical catheter to allow for bladder healing. So now, imagine undergoing A TURBT multiple times, and you can understand why the PRO

data suggests that patients really want a choice as an alternative.

So, given all the available data, how would I use UGN-102 if approved? Well, like all therapies, one size does not fit all. Every patient is different. UGN-102 provides a medical option for patients who have already had one or several TURBTs, and it gives me another option that I can discuss with my patients and share decision making.

I would use UGN-102 for patients with rapidly recurrent, low-grade intermediate-risk disease, such as those who are undergoing TURBT on a yearly basis or more frequently. UGN-102 would also be a very good choice for my older patients with multiple comorbidities, where general anesthesia may be a bit risky.

I view one of the main benefits of UGN-102 to be for patients whose bladders have obvious field defects, such as patients with innumerable small papillary tumors and those with so-called papillary carpeting of low-grade disease throughout

the bladder. In those patients, TURBT is unlikely to resect all the cancer, and for many of these patients, it's really just not feasible to resect 40 to 50 percent of a bladder.

I would not use UGN-102 in some specific circumstances: newly diagnosed bladder tumors, healthy patients with infrequent small recurrences, and patients with small solitary recurrences that can be full graded in the office or observed.

If approved, UGN-102 would provide my patients with a choice for treatment that achieves both long-term disease control and reduces the burden of TURBTs. My patients with recurrent low-grade bladder tumors are suffering, and the current standard of care treatment with repeated TURBTs is a burden to these patients that really does not effectively control their cancer. UGN-102 could profoundly improve cancer recurrence outcomes and urinary quality of life outcomes for many of my patients suffering from this disease.

Thank you, and now I will turn it back over to Mark Schoenberg.

DR. SPRATT: And if you can just be mindful of time because it's actually past time already.

Applicant Presentation - Mark Schoenberg

DR. SCHOENBERG: Thank you. I will.

Thank you, Dr. Kates.

Briefly, in conclusion, I'll offer a personal observation as a third generation surgeon.

For the past 25 years, I've treated patients with therapies that my late father, also a urologist, used to treat his patients. Imagine that, two generations with so little progress. Well, that can change today. I find these results incredibly compelling as a clinician, and our patients want and need options. That's what UGN-102 is. It's an option to come to the office, get treatment, and go about your day.

There aren't many opportunities in the lives of physicians to materially improve the treatment of a specific disease, but this is one of them. And it is a rare privilege to stand before you today and to ask for your help in making this opportunity a reality. Thank you for your

attention.

DR. SPRATT: Thank you to UroGen.

We will now proceed with the FDA's presentation, starting with Dr. Brian Heiss.

FDA Presentation - Brian Heiss

DR. HEISS: Good morning. My name is Brian Heiss, and I'm a medical oncologist and clinical reviewer in the Division of Oncology 1, Office of Oncological Diseases at FDA. Today, we'll be discussing the new drug application 215793 for UGN-102, mitomycin intravesical solution, submitted by UroGen Pharma. The applicant's proposed indication for UGN-102 is the treatment of adult patients with recurrent low-grade intermediate-risk non-muscle invasive bladder cancer or LG-IR-NMIBC. The members of the FDA review team are listed here, and my presentation reflects our collective input.

As Dr. Agrawal mentioned in his presentation, we would like to seek input from the committee on the following.

For discussion, given uncertainty regarding interpretation of durable response in LG-IR-NMIBC,

discuss whether randomized trials should be required in the future to assess the effectiveness of therapies in this disease setting; and the voting question, is the overall benefit-risk of UGN-102 favorable in patients with recurrent LG-IR-NMIBC?

My presentation today will consist of the following: a brief background on the NMIBC disease setting and key regulatory history; a summary of efficacy from two trials submitted by the applicant, ENVISION and ATLAS; a summary of data from these two trials, as well as a brief overview of patient-reported outcomes; and finally, considerations for the committee and the voting question.

First, I will discuss key background information.

To quickly recap the key disease background from Dr. Agrawal's presentation, with NMIBC, there's a low progression risk to muscle invasive disease; however, patients can recur frequently, resulting in repeated therapeutic interventions.

Low-grade intermediate-risk NMIBC is a heterogeneous disease and has wide recurrence and progression probabilities. This makes the natural history of this disease difficult to predict. TURBT with or without a single installation of intravesical chemotherapy is commonly used in practice to treat the disease.

Next, we move to regulatory history with this application. Please note that interactions with the applicant date back to 2016. I will discuss only pertinent regulatory history for brevity.

Prior to 2021, there were several meetings with the applicant to discuss various trial designs to support development of UGN-102 for the treatment of patients with IR-NMIBC. This included discussion of the randomized ATLAS trial of UGN-102 plus or minus TURBT versus TURBT alone. FDA reiterated that a non-inferiority design with a disease-free survival endpoint was not acceptable. In August 2021, FDA stated that an alternative single-arm trial design would potentially be

acceptable to support an application; however, with such a design, an ODAC discussion would be needed.

In November 2021, ATLAS enrollment was closed early due to a business decision. The FDA and applicant met again and had further discussions regarding a single-arm trial design to support an application. In February 2022, the single-arm ENVISION trial of UGN-102 had its first patient consented.

In September 2023, a presubmission meeting was held. FDA stated that primary results to support an application should be from the single-arm ENVISION trial, and ATLAS data may be considered supportive. FDA also reiterated the need for an ODAC discussion.

Now, I will discuss the results from the trials that provide evidence to potentially support efficacy.

This slide summarizes the primary evidence of efficacy submitted for this new drug application. As agreed, ENVISION is considered by the FDA review team to be the primary source of

evidence while ATLAS is a supporting source. ENVISION is a single-arm trial of UGN-102. ATLAS was a randomized trial of UGN-102 plus or minus TURBT compared to TURBT alone. Note that the patient populations between the two trials differ, with ENVISION enrolling patients with only recurrent LG-NMIBC now at intermediate risk, while ATLAS enrolled newly diagnosed or recurrent LG-NMIBC now at intermediate risk.

Overall, 240 patients enrolled in ENVISION of which 223 were considered evaluable for efficacy. In ATLAS, there were 282 patients enrolled of which 265 were evaluable for efficacy. For ENVISION, the primary endpoint was complete response rate, or CRR, at 3 months, and a key secondary endpoint was duration of response or DoR.

For ATLAS, disease-free survival, or DFS, was the primary endpoint; however, the DFS definition was problematic. CRR at 3 months and DoR were secondary endpoints in this trial. ATLAS was terminated early, making the endpoints exploratory only. ENVISION had 18 months of

follow-up.

Note that OPTIMA II, mentioned in the briefing document, is not considered by FDA as supporting efficacy evidence, as the interpretability of data from OPTIMA II is limited. The trial was a small, single-arm, proof-of-concept trial which differed from ENVISION in several key aspects. Patient population enrolled included both newly diagnosed and recurrent patients differing from their current only population in ENVISION. The primary and secondary endpoints were assessed for local review. Additionally, the follow-up was limited, only 9 months after CRR at 3 months. Although OPTIMA II is not being considered for efficacy, it can be used for the assessment of safety.

Additionally, the applicant proposed to include a small cohort of 8 patients who underwent home installation of UGN 102, which FDA concluded was not adequate to support efficacy; however, the cohort can contribute to assessment of safety.

First, the ENVISION trial. ENVISION is an

open-label, single-arm, multicenter trial that enrolled patients with prior LG-NMIBC treated with TURBT, currently assessed as having low-grade NMIBC by biopsy and had to have residual disease remaining, and had to meet criteria for one or two intermediate-risk features as listed here on the left. 240 patients were treated with UGN-102 once weekly for 6 weeks; however, FDA review identified 17 patients who did not meet eligibility criteria, and these patients were subsequently excluded, leading only to 223 efficacy evaluable patients. This was verified and agreed upon with the applicant.

The primary endpoint was complete response rate, CRR, at the 3-month visit based on cystoscopy, central pathology of any lesion, and central urine cytology. The key secondary endpoint was duration of response in those who achieved CR at the 3-month visit. Patients were followed every 3 months with cystoscopy, for-cause biopsy with central pathology review, and urine cytology, again, with central pathology review. The

definitions of complete response for the endpoints of CRR at 3 months and duration of response as listed on the bottom of the slide are reasonable.

Additionally, one clarification about DoR used throughout this presentation: to accurately represent the duration of response with limited trial follow-up, FDA evaluated the observed proportion of patients who remained in CR at a landmark time point, considering only those patients who were still being followed and confirmed to be in CR at that specific time.

Results from ENVISION in the FDA primary analysis population demonstrated CRR at 3 months of 77.6 percent; the 95 percent confidence interval lower bound, 71.5; and upper bound of 82.9. The reasons for not achieving a complete response at 3 months included residual disease, progression, indeterminate, or missing. Progression events included progression to high-grade TA, T1, and CIS, not muscle invasive disease. These events were rare. With respect to duration of response, 79.2 percent responding patients maintained

complete response at 12 months post the 3-month CR.

Another way to consider these results is that 61.4 percent of all patients treated with UGN-102 are found to have a resulting complete response at 12 months after the first disease assessment at 3 months.

FDA conducted subgroup analyses based on the intermediate-risk factors used for trial eligibility to assess the robustness of the CRR at 3-month results. These risk factors are shown here on the table on the left. CRR at 3 months was consistent across subgroups of patients with any one of the risk factors used to define intermediate risk in the trial.

With these ENVISION results, the following must be kept in mind for interpretation. CRR can be affected by intra- and inter-operator variability at cystoscopy and inter-reader variability of pathology; however, obtaining a complete response can be meaningful in clinical practice.

Interpreting CRR in the absence of a

concurrent control can be challenging. There's potential for selection bias, which can make extrapolating data to the broader LG-IR-NMIBC population difficult. An adequately conducted randomized trial could have potentially mitigated these concerns. While data from the randomized trial ATLAS was available, this trial was terminated early and had other issues that we will discuss next. However, CRR and DoR were secondary endpoints which allowed FDA to conduct exploratory analyses to attempt to address uncertainty with ENVISION. I will discuss these analyses next.

The ATLAS trial was a randomized trial that enrolled patients with either newly diagnosed or with a history of LG-NMIBC who currently were assessed as having low-grade NMIBC by biopsy and met criteria for one or two intermediate-risk features, as with ENVISION. The plan was to randomize 632 patients stratified by whether the patient had prior LG-NMIBC episode within one year, yes or no; however, due to the trial being terminated early, only 282 patients were randomized

1 to 1 to either 6 weekly doses of UGN-102 with an option for a TURBT at 3 months if the patient did not respond at 3 months or to TURBT alone.

Notably, patients were not scheduled to receive a single operative installation of intravesical chemotherapy or other additional intravesical therapy after TURBT.

FDA review identified 265 patients that met the prespecified eligibility criteria and were considered efficacy evaluable. The primary endpoint of DFS was to be tested first for non-inferiority followed by superiority. The key secondary endpoints were CRR at 3 months, duration of response, and those who achieved CR at 3-month visit, and patient-reported outcomes or PROs. Patients were followed every 3 months with cystoscopy, for-cause biopsy, and urine cytology, similar to ENVISION.

In considering ATLAS, the following limitations must be noted. Regarding the design, FDA did not agree with the applicant's DFS primary endpoint, as there were different definitions of

disease-free per arm. TURBT at 3 months was not counted as an event for the UGN-102 arm but was counted as an event for the TURBT-only arm. The non-inferiority design is problematic due to the difficulties in accurately determining the event time, establishing an appropriate non-inferiority margin in the setting. Furthermore, the non-inferiority design with the applicant's proposed different definitions of DFS per arm may show that two inherently different treatments are similar.

The control arm of TURBT alone lacked intravesical chemotherapy either as a single dose or followed by an induction course, which may underestimate the CRR in clinical practice. The PRO assessments differed in frequency between the arms, leading to interpretability issues. Regarding the conduct of the trial, the trial was terminated early, which resulted in it not being fully enrolled and with limited follow-up. I would like to note that for the purposes of this application, patient population enrolled in ATLAS

was different from ENVISION, and enrolled patients with newly diagnosed and recurrent low-grade NMIBC.

In order to consider ATLAS data as potentially supportive, FDA analyses excluded patients in ATLAS that did not match the ENVISION eligibility criteria; therefore, patients with newly diagnosed low-grade NMIBC and without a history of a prior low-grade NMIBC treated with the prior TURBT, as well as patients that were enrolled and not treated in ATLAS, were excluded to align the population to that of ENVISION. This resulted in 51 patients in the UGN-102 arm and 57 patients in the TURBT arm.

FDA exploratory analyses involved assessing CRR at 3 months in patients receiving UGN-102 in particular to consider whether the CRR at 3 months observed in ENVISION would be consistent in this second trial.

The baseline disease characteristics for patients meeting similar eligibility criteria in ENVISION and ATLAS are presented here. There are some minor differences in ENVISION compared to

ATLAS, such as more patients in ENVISION having multiple tumors and only one prior TURBT, and more patients in ATLAS having a previous LG-NMIBC episode within one year.

The FDA's exploratory analysis of ATLAS demonstrated a CRR of 72.5 percent in patients who had recurrent LG-IR-NMIBC. This appears to be supportive of ENVISION's reported CRR of 77.6 percent. There's a notable difference between the percent of patients who maintained a CR at 12 months post-3 months CR in ENVISION and in ATLAS. There were different follow-up times between patients with a CR enrolled in ENVISION and ATLAS, and since ATLAS was terminated early, the majority of patients did not have sufficient follow-up. Therefore, the percent of patients who maintained CR at 12 months post-3 months CR is difficult to interpret and does not provide support to ENVISION's DoR results with any certainty.

The CRR at 3 months in the TURBT alone arm in our exploratory analysis is 56.1 percent. The percentage who maintained a CR at 12 months

post-3 months CR was 21.9 percent; however, comparison of UGN-102 to TURBT in ATLAS is exploratory only. This was a post hoc subgroup analysis without formal hypothesis testing. Additionally, the TURBT arm lacked post-TURBT chemotherapy installation, which does not reflect the most active standard of care therapy.

Regarding durability at 12 months, there was limited follow-up, which makes the results difficult to interpret. Again, I must stress the comparison of UGN-102 to TURBT in ATLAS is exploratory only.

To summarize efficacy, evaluable patients in ENVISION had a CRR at 3 months of 77.6 percent, which was consistent with subgroup analyses and exploratory ATLAS results in a similar evaluable population. 79.2 percent of evaluable patients in ENVISION maintained a complete response at 12 months post the 3-month complete response; however, there are challenges in interpreting the duration of response in a single-arm trial.

As Dr. Agrawal noted, primarily it is

unclear whether duration of response observed is due to the effect of UGN-102 or the natural disease history. Comparison of UGN-102 to TURBT in ATLAS is exploratory only and likely underestimates the effect that would be seen with TURBT with intravesical chemotherapy, the most active standard of care.

With the last few efficacy slides in mind, let's discuss clinical meaningfulness of the 3-month CRR and DoR. Obtaining a complete response at 3 months can delay or potentially allow forgoing of additional therapy. The length of time responding patients maintain a complete response is key to whether it is clinically meaningful. The lack of a comparator arm in ENVISION limits interpretability, particularly for DoR.

We acknowledge that recurrence of disease results in subsequent intervention; however, the recurrence risk in this population is not well characterized, as it is unclear how many patients will require further TURBTs. So, the uncertainty and durability of UGN-102 leads to a lack of

clarity on what the expected recurrence-free interval is for these patients. So, a key question to consider is with UGN-102, while 1 TURBT may be avoided upfront by obtaining a complete response at 3 months, is this worth the associated toxicity?

I will discuss safety next. I will present the safety results from the submitted trials, as well as discuss the patient-reported outcomes.

To summarize the safety of UGN-102, let's examine the data from ENVISION and the pooled safety database for UGN-102, which is composed of safety results from the ENVISION, ATLAS, OPTIMA II, and BL010 trials. Generally, the safety was comparable between ENVISION and the pooled population.

In ENVISION, a little more than half of patients reported to have any grade adverse event. Overall, few grade 3-4 adverse events, serious adverse events, and treatment interruptions due to adverse events occurred. Very few treatment discontinuations were reported due to adverse events. One fatal event of cardiac failure

occurred within 30 days of last treatment; however, it is unlikely the event was related to study treatment.

The most common adverse events observed in ENVISION were genitourinary toxicity such as dysuria; urinary tract infection; hematuria; frequent urination; incontinence; urinary retention; and urethral stenosis. As shown in the table, these toxicities were mostly grade 1 and 2 in severity.

To further evaluate the development and persistence of toxicity while on treatment, we looked at the pooled incidence of lower urinary tract symptoms, or LUTS, using the applicant's group term for such symptoms, which includes multiple related genitourinary toxicity preferred terms, the most common being dysuria, incontinence, and urinary frequency. The figure on the left shows the breakdown of the incidence by LUTS by grade for the pooled population through the 3-month assessment. In total, 37 percent of patients experienced at least one adverse event of LUTS.

The majority were grade 1, but 9 percent of patients did have a grade 2 toxicity and 0.4 percent had a grade 3 toxicity.

Median duration of LUTS adverse events was 16 days during the time period, and 16 percent of LUTS events lasted greater than 3 weeks. The figure on the right shows the incidence by week and around month 3 with the incidence rate on the Y axis and treatment week on the X axis. Here we see that LUTS developed throughout the course of the 6 weekly installations, generally higher in weeks 4 and 5 and most resolve around month 3. However, these genitourinary symptoms are difficult to put into the context given the lack of a standard of care control arm.

The ATLAS trial, despite its noted limitations, can be used to examine the safety of UGN-102 in the context of TURBT in a similar patient population. Generally speaking, the majority of adverse events seen were genitourinary urinary events and, notably, these were seen at a higher rate in the UGN-102 arm. For example,

dysuria occurred in 30 percent of patients in the UGN-102 arm, while only occurring in 4.5 percent of patients in the TURBT arm, and events of urinary urgency, nocturia, and frequent urination were approximately 2 to 3 times more common in the UGN-102 arm.

Grade 3-4 adverse events also occurred at a higher rate in the UGN-102 arm than the TURBT alone arm; however, the comparison is limited, as it is likely confounded by unequal collection of adverse events between the two arms. Patients in the UGN-102 arm had adverse event collection at screening; then weekly for 6 weeks while receiving therapy; and again at month 2 by phone and month 3 in the clinic; while patients in the TURBT alone arm only had adverse events collected at screening, day 1/time of TURBT; and at months 1, 2 and 3, with the assessments at month 1 and 2 performed by phone.

This is a design flaw in the trial that cannot be corrected for. ATLAS was also not designed to adequately capture potential surgical

complication rates, anesthesia-related toxicity, or long-term toxicity associated with TURBT.

To summarize safety, in ENVISION, the most common adverse events were acute grade 1-2 genitourinary toxicities. The toxicity burden from 6 weekly intravesical UGN-102 installations may be greater than the toxicity burden from a single TURBT procedure. Furthermore, longer term toxicity data was not collected, and as a reminder, this is a disease setting with a low risk of progression to invasive disease and an overall favorable prognosis.

In ATLAS, there appears to be a higher incidence of acute genitourinary toxicities with UGN-102 compared to TURBT alone; however, ATLAS was not designed to capture surgical or long-term TURBT or anesthesia-related toxicity. The unequal safety assessment limits robust comparison between UGN-102 and TURBT, but given the provided data, UGN-102 has not been demonstrated to be a safer option compared to TURBT.

Patient-reported outcomes can provide

valuable information about the tolerability of therapy and symptoms of disease. Patients in both trials were administered the EORTC QLQ-NMIBC24, a questionnaire designed to capture symptoms for NMIBC, including urinary symptoms. PROs were exploratory in both ENVISION and ATLAS and should be interpreted with caution due to substantial limitations.

Specifically, PRO assessment strategy was incomplete, as assessment frequency did not fully capture time points of treatment side effects. In ATLAS, assessment was asynchronous between arms, and in ENVISION, there was potential selection bias, as PROs were only assessed in those who achieved a complete response.

Despite these limitations, FDA conducted exploratory analyses of the PROs. ENVISION is here on the left and ATLAS on the right. In both graphs, the Y-axis represents the mean change in urinary symptoms from the baseline and the X-axis represents the time point of assessment, week 2 through 6 and month 3.

In both the ENVISION and ATLAS trials, patients treated with UGN-102 exhibited progressively worsening urinary symptoms during the 6-week course of UGN-10; however, it is unclear whether the peak urinary symptoms were captured, as there were no PRO assessments between week 6 and month 3. Also, the trajectory and timing of side effect resolution was not captured, which could have provided helpful tolerability information. Overall, FDA concluded that the submitted PRO data are of limited utility in assessing the patient experience with UGN-102.

Now, let's conclude, looking at the overall benefit-risk from the data provided, considerations for the committee, and the discussion and voting questions. I'll provide a summary of the data submitted by the applicant to support this new drug application.

The single-arm ENVISION trial is considered by the FDA review team to be the primary source of evidence to establish efficacy. The CRR at 3 months was reported at 77.6 percent. Regarding

DoR, 79.2 percent of responding patients maintained a complete response at 12 months, which is assessed starting 3 months after a CR. The randomized ATLAS trial, while terminated early, is considered supportive based on exploratory analyses of CRR at 3 months. CRR at 3 months was 72.5 percent, and a subgroup of patients meeting eligibility criteria for ENVISION is consistent with the CRR at 3 months reported in ENVISION. Comparison of UGN-102 to TURBT in ATLAS is considered exploratory only.

Regarding safety, toxicity with UGN-102 primarily consists of genitourinary events that occurred throughout the 6-week treatment course and were low grade and reversible. Exploratory safety analyses from ATLAS suggests that the toxicity burden with UGN-102 is greater compared to the TURBT alone; however, as previously noted, the ATLAS trial was not well designed to compare safety or tolerability. And as I just mentioned, patient-reported outcome data was not collected in a manner that allows for adequate interpretation.

Given what has been presented, we would like

the committee to consider, can a durable CR assessed in a single-arm trial establish efficacy in a disease setting?

A CR may obviate the need for 1 TURBT but not necessarily future procedures. The prevention/delay of 1 TURBT is different from the prevention/delay of radical procedures. The length of time responding patients maintain CR is a key component of establishing clinical meaningfulness, but in a single-arm trial, it is difficult to distinguish between treatment effect and the natural history of disease when interpreting DoR. Furthermore, there's a lack of a well-established historical control.

There are additional uncertainties that I would like to briefly note. The long-term risks of recurrence/progression after UGN-102 are unknown. The outcomes for TURBT after UGN-102 are not well captured. The potential for resistance to therapies at progression is unknown.

We would like the committee to consider, is the overall benefit-risk favorable?

Toxicity appears more frequent with UGN-102 compared to TURBT. Patients undergo catheterization every week for 6 weeks versus one time for each TURBT. Genitourinary symptoms can persist or recur throughout and beyond 6 weeks. Toxicity is expected to be of shorter duration after 1 TURBT than with UGN-102.

Repeat TURBT may be difficult for some patients. There is potential of general anesthesia and cardiac risk, or potential bladder perforation, or other persistent genitourinary toxicities from the procedure; however, these events in the historical literature are rare, and there has been insufficient follow-up and data capture of these events in the applicant's trials to assess these risks.

An overall consideration is, does obtaining a durable complete response with UGN-102 at the expense of potentially increased genitourinary toxicity of longer duration than standard TURBT constitute a favorable benefit-risk profile in the face of the uncertainties that we have discussed?

We would like the committee to consider this question for discussion. Given uncertainty regarding interpretation of durable response in low-grade intermediate-risk non-muscle invasive bladder cancer, discuss whether randomized trials should be required in the future to assess the effectiveness of therapies in this disease setting.

Finally, we would like the committee to vote on this question. Is the overall benefit-risk of UGN-102 favorable in patients with recurrent low-grade intermediate-risk non-muscle invasive bladder cancer? Thank you for your attention.

Clarifying Questions

DR. SPRATT: Thank you.

We will now take clarifying questions to the presenters. When acknowledged, please remember to state your name for the record before you speak and direct your questions to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank

you and end of your follow-up questions with, "That is all for my questions," so we can move on to the next panel member.

Are there any clarifying questions for the presenters? And remember, use your little name taggy and point it upwards, and they'll record.

Dr. Vasan?

DR. VASAN: Neil Vasan. Thank you to the FDA and applicant for both presentations. This is a question for the applicant.

If you could bring up slide CE-15? I realize that the analysis of ATLAS is exploratory. There was a lot of dialogue about breaking up the cycle of repeated TURBTS and that this is a cycle, but I think what's clear here, and the FDA pointed this out, is it's that first TURBT that's being prevented. So you're not going from 4 to 1; you're going from 4 to 3 or 3 to 2. So that delta of the one TURBT that's prevented here, I'm trying to understand has that translated into anything from the PRO data or from the toxicity data.

I guess a corollary to that is that this

28 versus 22 that's shown here, we've heard that there was no intravesicular chemotherapy offered after TURBT, so I find it challenging to interpret if that's a real increase or if that's the same. So what do you mean by breaking up the cycle of repeated TURBTs given this data?

DR. LOUIE: Could I have the duration of response slide, please?

While we're waiting for that slide, I'll just address your second question first regarding the use of intravesical chemotherapy, and I'll ask Dr. Chang to come up in a moment.

Basically, we showed you the Sylvester data, which was a large meta-analysis of patients with intermediate-risk disease who had TURBT with or without single-dose intravesical chemotherapy, and they found that in patients with an EORTC score of 5 or greater, there was no impact on the risk of recurrence. The ATLAS trial patients, 75 percent of them had an EORTC risk score greater than or equal to 5.

Regarding breaking the cycle of TURBTs and

the avoidance of a single TURBT, I'd like to ask Dr. Kates to speak to that, and please pull up slide 2.

DR. KATES: Max Kates, Johns Hopkins. I mean, I think your point is exactly well taken. You have a medical therapy and you have a surgical therapy. And right at the outset, the ENVISION trial kind of proves out that the medical therapy obviates the need for the initial TURBT. So now the question is, does it obviate the need for a second TURBT? Meaning everybody would have had the first TURBT, so now we're asking the drug not just to obviate the need for one TURBT, but perhaps future TURBTs.

I think what I would actually look to is, basically, the slide I presented -- yes, if we could bring up slide 2, please -- that basically shows what do we have to show for that? Well, how many patients on study currently have yet to have a TURBT?

So, there are 21 months of follow-up to answer that question. And what we see from that is

that 81 percent of those patients remain in CR, so that translates to well over two-thirds of patients have not had a TURBT yet; that's of all patients, they have not had a TURBT. So, we can't answer the question beyond 21 months, but we can assume that the majority of those patients probably are not going to have a TURBT.i

DR. CHANG: Sam Chang, Vanderbilt. I was going to address the question regarding the use of perioperative chemotherapy and breaking the cycles we've discussed.

The use of perioperative chemotherapy, the results and effectiveness are, in fact, mixed, and that's why the guidelines actually really dedicated the use of the word "considering" as opposed to "recommending" or "mandating." Understand the use of perioperative chemotherapy is most effective for primary tumors and solitary tumors, very different from the patient populations both in ENVISION and ATLAS, where the efficacies, in fact, do not show much benefit, and that's the Sylvester curve. If you bring up the Sylvester curve as well, you can

see the differences between intravesical treatment versus no treatment, and the recurrence rates are basically quite similar.

A point that hasn't been raised, if I could add, is that perioperative chemotherapy is dependent upon safety, and there are very few times in a guideline that it states that you should not do something. And specifically for TURBT, if there's concern regarding a deep resection or perforation, in fact, it's really recommended that you do not give perioperative chemotherapy. So those risks and the possible side effects associated with that are eliminated by the fact that you don't have a TURBT with this agent. Thank you.

DR. VASAN: Thank you.

DR. SPRATT: Tara Frenkl?

DR. FRENKL: Tara Frenkl, non-voting industry rep from Bayer. I had a question, actually for the FDA, to understand a little bit more context in thinking about the study design of ATLAS. One of the points of discussion was the

appropriate endpoint for doing a non-inferiority study versus a superiority study, where it seems to me the intention of this is not to be superior to TURBT necessarily, but to offer another option.

So my understanding from the book was that OS would be the most appropriate for a non-inferiority design, but it's not really applicable in this disease setting. So I'm just wondering if you could give a little more context on how you're thinking about that.

DR. SUZMAN: Sure. Daniel Suzman, FDA. As you mentioned, guidances and effect regarding endpoints, for a non-inferiority trial, we need an event that has a hard date; for example, overall survival. We've also used response rate for non-inferiority trials.

The difficulty with a time-to-event endpoint that has variability regarding the assessment, such as a disease recurrence, it means that a sloppy trial conduct is more likely to demonstrate non-inferiority, and that creates a lot of issues in interpreting the the outcome. The other issue

with a non-inferiority trial in this specific disease setting is that there is insufficient historical data regarding what the margin is or should be.

DR. SPRATT: Dr. Madan?

DR. MADAN: Ravi Madan, National Cancer Institute. This question is for the sponsor. I'm just wondering what your view is of -- you make a very compelling case for the need for these types of therapies in this space.

What are the obstacles at this time for running a randomized trial in this space? And now that you have data from what you've presented this morning, are you able to model what a randomized trial would look like? And would that be smaller than the ATLAS trial, making it more, I guess, nimble and feasible?

DR. LOUIE: Yes. I think when you're considering potentially running a randomized controlled trial, there are a couple of things to think about. First of all, there are no approved drugs for immediate-risk disease, so there's no

direct drug for us to compare against. The standard of care is surgery under general anesthesia, and you could have an unprecedented regulatory bar to show superiority of a drug to a surgery.

Single-arm trials have been discussed in the FDA 2018 guidance, which said that complete response and duration of response in single-arm trials are valid measurements of efficacy, and single-arm trials have also served as the basis for multiple approvals in non-muscle invasive bladder cancer.

I'd like to ask Dr. Kates to please discuss his view on single-arm trials and utilizing those results in non-muscle invasive bladder cancer.

DR. KATES: Max Kates, Johns Hopkins. As an investigator and a study chair of both single-arm and randomized controlled trials, I'll say that besides the fact that the FDA has approved three other drugs for NMIBC based on single-arm trials, this is actually in a very different disease space where there is an existing tumor that's then being

ablated.

So unlike the three trials in which the tumor was resected, and then the drug was given, in this situation, the drug is still in the bladder. So talking about natural history, the natural history of a tumor, that then you do a cystostomy 3 months later, it's 100 percent that the tumor will still be there.

DR. SPRATT: Sorry to interrupt, but can you just address the question that was asked about the feasibility and the sample size of running the trial, not the prior FDA-approved therapies?

DR. KATES: I will let the sponsor answer that question.

DR. LOUIE: Dr. Berger, can you come up and address this about the feasibility and sample size?

DR. BERGER: Brent Berger, biostatistics, UroGen. I think that topic would actually have to be discussed with the agency regarding what type of hazard ratio, for example, that would be appropriate to pursue.

DR. MADAN: Thank you.

DR. SPRATT: FDA?

DR. SUZMAN: Daniel Suzman. I just want to quickly respond to Dr. Kates' point around single-arm trials and complete response rate.

Just to clarify, the approvals in later line or high-risk setting of BCG unresponsive, NMIBC is specifically in patients with carcinoma in situ in which you can assess complete response, basically, the assumption is that the disease is still present in the bladder, and that the absence of disease at subsequent assessment is evidence of drug activity. And again, the difference in this disease setting is that the procedure that is being delayed or prevented is one of very different morbidity and mortality than radical cystectomy.

DR. SPRATT: Thank you.

Any other clarifying questions?

Yes, Dr. Gradishar?

DR. GRADISHAR: Bill Gradishar from Northwestern. I guess in follow-up to Dr. Suzman, I was just trying to get a sense, in this age group, and thinking about the possibility of doing

a randomized trial, and having sufficient follow-up in a population with significant comorbidities, what would you envision the drop-off over time, getting to the issue of feasibility?

DR. SUZMAN: Daniel Suzman, FDA. I think that's ultimately a question that needs to be discussed with the sponsor and with each individual disease setting, rather than one we can address today. I think we've seen with the ATLAS trial, that it does appear to be feasible to run a randomized trial of TURBT versus the intravesical drug. Study conduct I think is one that we'd have to look at during the design phase and during the conduct of the trial. I can't give you a number offhand.

DR. SPRATT: I have a question. This is Dan Spratt from UH Seidman, Case Western Reserve. This will be to one of the clinical experts with the sponsor.

There was no central pathology required to go on this study. I'm not a pathologist, and trying to do reading, it looks like the agreement

of general pathologists, expert pathologists, the kappa is around 0.6. And I just wonder, is this something that you believe -- what's your confidence that the patients that truly were enrolled on this trial were this low-grade intermediate risk?

I'll follow that up with a second question to the sponsor after that, but if one of the clinical experts could speak to that.

DR. LOUIE: Dr. Chang?

DR. CHANG: Sam Chang, Vanderbilt.

Dr. Spratt, an important question when looking at bladder cancer because it can be difficult from a pathologist standpoint. But the difference between cancer/non-cancer is not very difficult. The difference between high grade and low grade, not very difficult. The difference between TA tumors, urothelium, versus T1/T2, not very difficult.

What I mean by that is the subtleties when reading pathology really are dependent upon deeper tumors or where there's some intermediate risk type

grade. So when confining a population, again, trying to make a heterogeneous population as homogeneous as possible, low-grade TA is probably one of the easiest distinctions, both centrally and in the community. Thank you.

DR. SPRATT: Great. Thank you. That answers that question.

The other question I have -- again, this is Dan Spratt -- is, to have a response, it was a cytology as well as the visual inspection or cystoscopy, potentially a biopsy. And I was just curious, how many patients actually underwent a biopsy versus it was just visual inspection?

DR. LOUIE: Dr. Raju, can you please come up?

DR. RAJU: Sunil Raju, Clinical Development, UroGen Pharma. So in total, there were just over 100 patients who underwent a biopsy for potential recurrence or progression. And in the vast majority of cases, these were assessed based on central pathology and central urine cytology as well. And this was either at 3 months or during

the follow-up period.

DR. SPRATT: What was at that 3-month mark? How many of the biopsies were negative?

DR. RAJU: In terms of at 3 months, we had 42 that were done at 3 months. And we don't have the exact numbers, but majority of them were done via central pathology. And overall, when we did an assessment for concordance, where we got the local samples back, there was no change to any of the overall efficacy conclusions.

DR. SPRATT: Okay. Appreciate it. Yes. What I'm getting at is, the visual inspection of response, is that a very robust measure of response? And it sounds like they're pointing to someone they'd like to speak to this.

DR. LOUIE: We'd like to ask Dr. Kates to respond, please.

DR. SPRATT: Especially given, I think it was, Dr. Chang, your presentation that said after a TURBT, a lot of the time, there's still tumor left behind. So how great is just visual inspection? Are you overcalling response?

DR. KATES: Max Kates, Johns Hopkins. The visual response at 3 months is the typical way response is evaluated on all clinical trials, and it is one of the reasons why we like to see durability, which was shown. Because if patients are undergoing cystoscopies every 3 months, even if there's an incredibly subtle lesion that, say to your point, might be missed on visual cystoscopy, it will prove out over the course of the subsequent cystoscopies.

DR. SPRATT: Thank you.

If no further questions from anyone, then we will have a 15-minute break because we can't move up the OPH, open public hearing, too early just because they're scheduled or moving it up a little bit.

So we will take a quick 15-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume at 22 after; is that ok? Twenty-two after, and I will start it immediately

at 22 after. Thank you.

(Whereupon, at 10:08 a.m., a recess was taken, and meeting resumed at 10:23 a.m.)

Open Public Hearing

DR. SPRATT: Welcome back. We will now begin the open public hearing session.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the industry group. For example, this financial information may include the industry group's payment of your travel, lodging, or other expenses in connection with your participation in the meeting.

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

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

For those presenting virtually, please remember to unmute and turn on your camera when your OPH number is called. For those presenting in person, please step up to the podium when your OPH

number is called. As a reminder, please speak only when recognized by the chairperson. Thank you for your cooperation.

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

MS. LAGO: Good morning. My name is Yazmin Lago, and I'm here as the wife of Julio Lago and as a caregiver. I don't have any financial relationship with the company for this session. I'm not a doctor or a scientist. I'm a wife, a mother of three daughters, and someone who walks alongside my husband through this cancer journey. I'm happy to have been asked by UroGen to share our story.

Julio has submitted his written testimony as well, where he shares his experience as a patient. I wanted to be here to share my own journey from the caregiver perspective, as a caregiver and as someone whose life was deeply affected by his illness and by the hope that came with UGN-102.

Before UGN-102, our lives revolved around

the painful cycle of surgeries and recoveries. Every time the cancer came back, we had to go through all of it again, the procedures, the waiting, the worry, the uncertainty. I took time off work, and we had to ask for help taking care of our three daughters, and it affected every part of our life.

Julio's recoveries were long and hard. He lost his energy. He stopped doing the things he loved, like running. And as a strong presence inside of our household, seeing him so worn out was really difficult for all of us. We were always on edge, wondering if or when the cancer would return again.

When his doctors suggested UGN-102, it felt like a light at the end of the tunnel. We were hopeful but nervous, too. The decision to accept enrolling in the trial required discernment, and it came with a lot of uncertainty as well. We didn't know if it would work, but they gave us a reason to hope. I'm so grateful that we got to the right doctor at the right time, who offered his opinion

instead of continuing down with the path of more surgeries and recoveries.

I went with him to the first few treatments, but after that, he was able to go on his own. It wasn't like surgery at all. He would come home, walk around, eat dinner with us. Within a few days, he was even running again. He runs half marathons. Seeing him bounce back so quickly felt like we were getting pieces of our old life back.

After a few months, we got news that the cancer was gone. It was such a relief. We hadn't felt that joy in a very long time. Our daughters noticed the change as well. The mood in our home shifted from fear and stress to something lighter, more hopeful. UGN-102 didn't just help Julio physically, it helped bring our family back to our old life, our old ways. It gave us normal days again, and that for me was everything.

I know Julio's story is in his written testimony, but I wanted to share the caregiver side because this treatment helped our whole family, not just him. It gave us hope, time, and peace that we

hadn't had in a long time. I respectfully ask you to approve UGN-102 so other patients and caregivers like us can now have the same chance to move beyond fear, to heal, and to get their lives back. Thank you so much.

DR. SPRATT: Thank you so much.

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

MS. MALZONE: Hi. My name is Lisa Malzone, and I'm here today to share my experience as a patient who participated in the UGN-102 trial. I am not a medical professional; I am just someone who went through this personally, and I'm incredibly grateful that I did.

Like many women, I spent a long time misdiagnosed with UTIs. For almost a year, I was going to the doctor, regularly, being told it was just infections. I did not know anything was seriously wrong until I started bleeding while on vacation. That was when I finally went to my primary care doctor and said, "Something isn't

right." He sent me for an ultrasound, and that's when they found the tumors. I was lucky to be referred to Dr. Prasad right away. He confirmed the diagnosis and scheduled my first surgery. The surgery went well, but then the cancer came back. That's when Dr. Prasad talked to me about the UGN-102 trial. He said I was a good candidate because the cancer hadn't penetrated the deeper layers of my bladder.

My husband and I agreed to move forward with the trial. The treatment itself was incredibly manageable. Once a week for 6 weeks, I'd go for my appointment. The staff would take my blood, check my vitals, and then administer the treatment, but they would administer the treatment directly into my bladder. It wasn't painful; it was just cold. And when the medication went in, it was an interesting feeling. I could have gone back to work the same day, and it didn't interrupt my life at all.

That's why I want to emphasize that this treatment didn't take over my life. I didn't feel

sick, I didn't lose time with my family, and I didn't lose any time at work, and as a patient, that means everything. I did have a small reoccurrence a while ago, and I ended up being let go of the trial, but recently I went back for my follow-up cystoscope. It was clear, and now I get to move to yearly checkups. That's a huge milestone, and something I never imagined would be possible from the first diagnosis.

Every time I see Dr. Prasad, we talk about how important it is for patients like me to have options like UGN-102. Not everyone can keep going through surgery after surgery. This gave me another way forward, and I truly believe that other patients deserve the same chance. Thank you for listening, and thank you for considering the approval of UGN-102. It made a difference in my life, and I believe it can do the same for many others. Thank you.

DR. SPRATT: Thank you so much.

Speaker number 3, please state your name and any organization you are representing for the

record. You have three minutes.

DR. PRASAD: Good morning, and thank you for the opportunity to speak today. My name is Sandip Prasad. I'm a practicing urologic oncologist and the Director of General Urinary Oncology at Morristown Medical Center in New Jersey. I'm a community-based urologic oncologist. I was also the primary investigator on the ENVISION trial, evaluating UGN-102, and I serve in various advisory services to UroGen Pharma.

You've all reviewed the data today, and I think it speaks for itself, a complete response rate of 77 percent; durability at 12 months for those that are disease-free of 83 percent. I really want to speak from a urologist perspective. You heard from one of my patients already, Lisa, today, and I just want to speak about this from our perspective in regards to surgical options.

This disease, low-grade intermediate-risk disease, it doesn't make headlines. It's not a disease that necessarily progresses towards major operations like cystectomy, but it does have a

significant consequence on patients, and it does for urologists as well. For many of these patients, they were on systemic blood thinners, they have COPD, other comorbidities. We have to manage these patients to take them to the operating room. This requires discontinuation of blood thinners, which for many patients is not necessarily risky but causes anxiety both to them and to their primary providers.

So these are elderly patients. General anesthesia carries a real risk. Surgical scheduling carries delays. Recovery adds strain to these patients. And unfortunately, still, in many of these patients, tumors come back. Really, what we need and our patients need are options. UGN-102 is not a replacement for TURBT in every single patient, but it represents a genuine alternative for us, for patients who've been through multiple resections or for whom surgery is just simply more risky than a benefit for these patients who recur.

It can be given in the office with a catheter, without anesthesia and, importantly, it

treats everything in the bladder. It's a field treatment for the bladder, and not just what we can see, and this allows, I think, to treat tumors that we cannot otherwise visualize. It's very well tolerated, logistically manageable in our offices, and backed by outcomes that are really superior to what we see in this space historically.

I've been practicing long enough to know that not every therapy makes a difference in practice immediately, but I really believe that UGN-102 does. I had several patients in the ENVISION trial, and I saw the relief on their faces when I was able to treat them and offer them a break from the cycle of recurrence. For them, and for many others like them, this treatment matters. I strongly believe that UGN-102 deserves to be a treatment option. I thank you for your time.

DR. SPRATT: Thank you so much.

Speaker number 4, please state your name and any organization you are representing for the record. You have three minutes.

(No response.)

DR. SPRATT: Sorry. Mr. Perlin, you are muted. If you could unmute.

(No response.)

DR. SPRATT: We still cannot hear you.

Can you guys unmute him?

DR. SEO: This is Jessica speaking.

Dr. Spratt, I think our team can work with speaker 4 to figure out how to unmute himself, and then we can circle back to speaker 4 at the end, if that's ok.

DR. SPRATT: That sounds great.

So we'll come back to you, Mr. Perlin.

We're going to move on to speaker number 5. Please state your name and any organization you're representing for the record. You will have three minutes.

MR. HYLAND: Good morning. I'm very happy to be here today at this important meeting. My name is Thomas Hyland. I'm 87 years old. I'm here to share my personal experience with bladder cancer and as a participant in the UroGen 102 ENVISION clinical trial.

A little about me, I was born in North Jersey. I went to high school, got married at 30, raised three children, and spent many years in the auto industry. In my spare time, most of my spare time I spent with the Missionaries of Charity, which was founded by Mother Teresa, and it was a great honor spending time with her on several occasions.

My bladder cancer began in 1992 when I noticed blood in my urine. It would come and go at first, and I really didn't take it seriously, but over time, it kept happening, and I finally saw a urologist. I was diagnosed with low-grade intermediate-risk non-muscle invasive bladder cancer.

From that point on, my life became a cycle of procedures. For many years, I underwent regular cystoscopies. If they found tumors, they'd scrape or catheterize them. Eventually, I was having TURBTs surgeries every 3 to 4 months and for probably close to 15 years. These were invasive and disruptive physically and emotionally. After

each procedure, I experienced some bleeding, loss of urinary control, and I was frustrated. I felt like I was just managing a never-ending pattern of recurrence with no real long-term solution.

That changed when I was referred to Dr. Sandip Prasad and introduced to the UGN-102 trial. I was hopeful. After years of undergoing surgeries, I was eager to try a treatment that didn't involve another TURBT, something that might actually stop the cycle of recurrence. When he called me to ask me, I was so happy to be able to do it.

That changed when I was referred to Dr. Sandip. I was hopeful in years of undergoing surgery and eager to try treatment that didn't involve TURBTs. Participating in a trial gave me more than just medical care. It gave me hope, stability, and the opportunity to focus on the things and people I love without constantly worrying about the next surgery.

As a patient, it was a very simple and easy procedure, no problems in administering, no after

effects. It was great. It was wonderful, and I was very encouraged that it was going to work. Participating in the trial gave me more than just medical care. It gave me hope, stability, and ability to focus on the things and people I love

As a patient, I can't speak to the science of UGN-102, but I can speak to what it meant to me. It offered a real alternative to the cycle of repeated surgeries. It gave me back control and peace of mind. I believe patients like me -- older and living with recurring bladder cancer, and trying to maintain a good quality of life -- deserve options that are less invasive and more sustainable. I am grateful that I had the chance through this trial and treatment with UGN-102.

I'd also like to say that part of this trial was not just helping myself; it was for helping others. Every patient is different. We all have unique medical histories, personal responsibilities, and goals for how we want to live. We should have access to options that are

aligned better with our needs and quality of life, giving patients the opportunity to choose what is right for them, whether it's less invasive treatments, clinical trials, or newer therapies, giving them dignity, control, and hope.

I'm here today because I had that choice, and I hope that more patients will have the same opportunity in the future. Thank you again for listening and for the important work you do to make voices part of this process.

DR. SPRATT: Thank you so much.

MR. HYLAND: Amen.

DR. SPRATT: Appreciate it. Amen.

MR. HYLAND: Thank you.

DR. SPRATT: So we're going to try to go back, if we can, to speaker number 4. Please state your name and any organization you are representing for the record. You have three minutes.

MR. PERLIN: My name is Mark Perlin, and I'm not representing anybody involved in today's hearings.

DR. SPRATT: You may continue.

MR. PERLIN: Thank you.

I'm here to share my experience as a bladder cancer patient, and although I'm not eligible for UGN-102, I want to speak on behalf of patients who may benefit from this treatment, and, importantly, to highlight the toll that repeated TURBT surgeries can take on a person's life.

I was diagnosed with bladder cancer in January 2018 at age 67. I had no symptoms at all. My cancer was discovered only because a cystoscopy was performed following a prostate procedure. Without that routine check, I may not have known I had cancer until it was far more advanced or even too late.

Over the next three years, I went through four separate TURBT surgeries, each one becoming harder than the last, physically, emotionally, and mentally. My first TURB was in February 2018. At that time, I believed it might be the end of the road with cancer, but just a few months later, in June, I was back in the operating room; then again in 2020, in the middle of the COVID pandemic when

hospitals were overwhelmed, and I had to go through it completely alone. My fourth TUBRT came in 2021.

These repeated surgeries didn't just affect me, they disrupted my life and placed a heavy emotional burden on my family. I missed important events with family and friends on more than one occasion. I had to miss two weddings and also had to cancel or postpone several trips because of procedures, recoveries, and monitoring.

The thought that there is a treatment that can address NMIBC without surgery is one that I would have been thrilled to have available to me. Going into surgery is never easy emotionally, even with a great support system. I had that. My wife was a nursing instructor for many years at Bellevue Hospital in New York. I have close friends in nursing and social work, and I was fortunate to have their support. But the bottom line is this. You're alone when you're on the operating table, alone with what's going on in your head, and that feeling doesn't go away.

So while I'm not a candidate for UGN-102, I

understand deeply what patients with bladder cancer go through. I know the anxiety of waiting for scan results, preparing for another surgery, and recovering while wondering when the next one will come.

A non-surgical treatment like UGN-102 could be life-changing for people with low-grade bladder cancer. It can mean fewer disruptions to their lives, more time with loved ones, and less physical and emotional strain. It's not just a medical advancement; it's a chance to improve quality of life and restore peace of mind. I urge you to consider what UGN-102 represents, not just in terms of the data, but in terms of human impact. Thank you for listening.

DR. SPRATT: Thank you so much.

Alright. Speaker number 6, please state your name and any organization you're representing for the record. You have three minutes.

MS. DEOUDES: Good morning. Thank you, members of the committee, for the opportunity to speak today. My name is Meri-Margaret Deoudes, and

I'm the Chief Executive Officer of the Bladder Cancer Advocacy Network or BCAN. For 20 years, BCAN has been the voice of bladder cancer patients and families. Everything we do is focused on creating better todays and more tomorrows for the more than 725,000 Americans living with bladder cancer and 84,000 newly diagnosed each year. Tragically, more than 17,000 will lose their lives to this disease in 2025 alone.

Bladder cancer is the seventh most common cancer in the United States and, sadly, fourth amongst our veterans. Incidence rates are also rising in some populations, especially among women. Moreover, due to its frequent reoccurrence, as already mentioned, bladder cancer is among the most expensive cancers to treat over a patient's lifetime, creating significant financial and psychological stress for patients.

About 70 percent of cases are non-muscle invasive bladder cancer, or NMIBC, a form that reoccurs often and forces patients to undergo repeated invasive procedures, as also already

noted. For decades, the standard treatment has been the TURBT. While this saves lives, it's invasive, requires anesthesia, and carries risks, especially for older adults. Additionally, the procedure has changed little in decades, leaving patients with few options.

That is why BCAN strongly supports new treatments that offer safe, effective alternatives. UGN-102 has shown promise in clinical trials for patients with low-grade intermediate-risk NMIBC and may reach tumors that a TURBT would miss and reduce the need for repeated surgeries. For patients and families, new and better treatment options are always good news. More options mean more hope, less uncertainty, and overall better quality of life.

On behalf of the bladder cancer community, I thank you for your commitment to improving patient care and for hearing our voices today. We respectfully encourage you to recommend approval of UGN-102 and bring this much needed innovation to the patients who need it most. Thank you.

DR. SPRATT: Thank you so much.

Speaker number 7, please state your name and any organization you are representing for the record. You have three minutes.

MS. PARKER: Good morning. My name is Lacey Parker. Thank you for the opportunity to speak today. I am sincerely grateful to UroGen for supporting my travel from California to here. It's important to me to be here today to be part of this conversation.

I have had, since 2016, low-grade intermediate-risk non-muscle invasive bladder cancer, and for years my life was shaped by this disease. My cancer would reoccur every 3 months like clockwork, so that just meant another surgery, another TURBT, and it just continued on. The toll it takes going through pre-op, and then anesthesia and the surgery, and rides to and from, and the recovery time, and the time missed from work, it takes a toll.

Even though my cancer was low grade, it had a really high impact on my life. It was always

there, hanging over me, disrupting my plans, and leaving me constantly in fear and on edge. I really never felt free or relaxed. It was like I was always bracing for the next round. Then I joined UGN-102, and everything changed for me. When my doctor said that that was available, I just remember the moment like something was finally there to help me.

Since starting treatment with UGN-102, I've been cancer-free for 2 and a half years. That's the longest I've ever gone without a reoccurrence; no surgeries, no anesthesia, no missed work. And it just gave me the freedom back in my life to enjoy my children and my grandchildren, and to be able to work without all the repeated surgeries.

What most excites me about this, not only for myself, is what it can do to help other people, especially older patients, which for whatever reasons, medical or personal, they can't go through surgery after surgery. They're older. That's when I got really passionate about this, when it could help others that couldn't go through all the

surgeries like I did. So I'm standing here today because I want others to have the same opportunity I did. I want them to have access to the treatment that works and that fits into their lives without turning everything upside down.

Thank you for listening to my story, and I hope this helps for you to see the real human impact that UGN-102 can have.

DR. SPRATT: Thank you so much.

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

I'll briefly ask if there are any remaining clarifying questions.

(No response.)

Questions to the Committee and Discussion

DR. SPRATT: Thank you.

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'll 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. After I read each question, we will pause for any questions or comments concerning its wording.

We will proceed with our first question, which is a discussion question. Given uncertainty regarding interpretation of duration of response in low-grade intermediate-risk non-muscle invasive bladder cancer, discuss whether randomized trials should be required in the future to assess the effectiveness of therapies in this disease setting.

If there are any questions on the interpretation of this question, please let me know now.

(No response.)

DR. SPRATT: If there are no questions or comments concerning the wording of the question, we'll now open the question to discussion. And you can use your name tag, and we'll record. And I will definitely be asking from our urology

colleagues their insight into this, so if either Dr. Garraway or Dr. Ball want to comment.

Dr. Ball?

DR. BALL: Mark Ball, National Cancer Institute. I think we've heard a number of critiques of the data presented today that could have perhaps been mitigated by having a randomized trial. That being said, though, there seems to be precedent in this disease space to use a single-arm trial design. So while it's always the highest degree of evidence to have a randomized trial, I think saying it should be required is up to interpretation. I don't know that it's required, although it is preferable.

DR. SPRATT: Thank you.

Dr. Garraway.

DR. GARRAWAY: Thank you. Isla Garraway, urologist. I agree with the comments of my colleague, Dr. Ball. I think it's very clear. I think all of us would agree that randomized clinical trials are the gold standard, still, and really allow us to have better insight into the

efficacy of therapy, and the duration of response is the particular question here. But having said that, I do feel like the single-arm trial design, with the evidence presented, was somewhat compelling, and they shouldn't be ruled out as a potential for evaluating this question in the future; although, of course, I think our first choice would always be a randomized clinical trial.

DR. SPRATT: Thank you.

Dr. Conaway. Dr. Conaway?

DR. CONAWAY: Mark Conaway, University of Virginia. I took this as a general question, not necessarily specific to this particular application. We have seen single-arm trials, and they're typically in situations where randomized trials are infeasible, where it's a rare cancer. So accrual would be an issue where there's no clear endpoint decided on or where survival or recurrence events are so rare, again, to make sample size infeasible.

It doesn't seem like this is the situation here. We have a relatively prevalent cancer,

relatively high risk of recurrence. This seems like, for the statistician on the board, the ideal randomized clinical trial setting, and I'm struggling to understand -- I understand the word "required" may be a bar that's fairly high, but I don't understand why clinical trials in this setting wouldn't be required.

DR. SPRATT: Yes?

DR. PAZDUR: Can I just clarify? This is a future directing question.

DR. SPRATT: Can you state your name?

DR. PAZDUR: Oh. This is Richard Pazdur, FDA. I think the intent of this question was future looking, not the results of this trial and what we'll do with this application. But here again, you have a very common disease here, which a randomized trial can be done.

Let's look at what a single-arm study gives you. Basically, it gives you a response rate, and that's it, so to speak, with any confidence. You had a large number of patients that were enrolled in this trial, a single-arm trial over 200, and all

the additional patients give you is just precision around a response rate, basically. It does not allow you to look at a time-to-event endpoint such as disease-free survival, time to progression or overall survival, and adequate, really, assessment of duration of response, and adequate assessment of toxicity, and adequate assessment of patient-reported outcome.

So we get so much more from a randomized trial, and that's why our emphasis was, ok, where did we want to go in the future with this disease?

DR. SPRATT: Thank you.

Dr. Vasan?

DR. VASAN: To, I guess, maybe provide some more color as well, when I'm thinking about this, I was thinking about the the approval of mitomycin in upper tract disease, where the disease is very rare -- I think that's been acknowledged -- and the surgery is very morbid compared to a TURBT. So I echoed some of Dr. Conaway's comments about that it seems like a great disease space to do an RCT.

One thing that was compelling by the OPH

comments as well -- and I think we've seen this in other products as well, where sometimes these events that are very meaningful for patients are very hard to quantify. I'm thinking about something we've had prior discussions about with other drugs, transfusion dependence, and how that can be sometimes very hard to quantify, but it is meaningful.

I'd like to understand from Dr. Garraway and Dr. Ball, we've clearly heard the benefit for patients of not needing this additional surgical procedure. I do think that a randomized controlled trial would be able to capture what that means in terms of additional endpoints and safety endpoints, but how do you see this in the real world, and the types of patients, and the number of patients who would benefit from this versus standard of care?

DR. SPRATT: Dr. Garraway?

DR. GARRAWAY: Hi. Isla Garraway. I appreciate that question. As a urologist practicing in the VA population, which is an older population with a lot of significant comorbidity,

certainly a TURBT requires general anesthesia, in general, and in patients with comorbidity, the complications from that are real, in terms of the general anesthesia complications, and even just getting to the OR and stopping medications like you've heard today.

So I do think that having another option that's less invasive that can be done in the clinic is ideal for this older population on the patients that it affects. So I do think it definitely would be a benefit to have an option in this case.

DR. SPRATT: Dr. Ball?

DR. BALL: I would echo my colleague's comments.

DR. SPRATT: State your name.

DR. BALL: Mark Ball, National Cancer Institute.

DR. SPRATT: Thank you.

DR. BALL: I would echo my colleague's comments. The toxicity data from the ATLAS trial, I don't think we really have the granularity to talk about the toxicity of TURBT. Sure; many

patients can do well after TURBT, but the downside for bad outcomes is quite high. Many patients with comorbidities can be hospitalized for multiple days, and it's something as practicing urologists we see with some frequency. So having a non-surgical alternative for these high-risk, high morbidity patients is very appealing.

DR. SPRATT: I'm going to jump to our patient representative, Colette Johnston.

MS. JOHNSTON: Yes. I just wanted to go back to the discussion of the randomized trials being required. And believe me, I'm a big fan of randomized trials. I understand the benefit of the data retained from them, but I get hung up on the word "required."

I think that we need to look at these on an individual case-by-case basis, and if that requirement is going to prevent a drug that has potential for great benefit from moving forward due to recruitment, or multiple other obstacles that could be put in place on a required randomized trial, I feel like it's important that we address

this question moving forward. It's a great question. And like I said, big fan of randomized trials, but I don't like the word "required" in this. Thank you.

DR. SPRATT: Thank you.

Dr. Madan?

DR. MADAN: I think that --

DR. SPRATT: Introduce yourself.

DR. MADAN: Sorry. Ravi Madan, National Cancer Institute. Apologies, Dr. Spratt.

I think in this setting where you have the potential for great heterogeneity and also the potential for an indolent disease process, it heightens the need for us to have a randomized data set so that we can control for these variables for stratification.

I also think that -- I don't know much about this disease state, but I was educated on this more by the great presentations today -- you could envision, in a way, that you can do a study like this because of the nature of the disease, where it is somewhat patient friendly; because I know that

there are some apprehensions about trials where people are randomized not to the treatment, but you could have a landmark analysis where there's a potential for crossover, and then collect even more data.

So I think that this disease state does potentially lend itself, more than some other disease states, to a randomized approach, and one that could be patient friendly and correct for heterogeneity.

DR. SPRATT: Thank you.

I'm Dan Spratt, UH Seidman, Case Western Reserve University. As the question's written, in this specific disease space, in the future, I would strongly agree that randomized trials are necessary. We can easily foresee -- it's not up to this ODAC to determine is this going to be approved or not. That's not the question. But let's just say this is approved and this is the bar. You're going to all of a sudden have many therapies that just simply need to hit a 3-month response rate.

If you look at even the ENVISION trial,

there are only 2 patients at risk at 2 years. So we're talking about a very indolent disease. No one's dying, no one's getting cystectomies, no one's metastasizing. It doesn't mean there's not morbidity, as we've heard from patients. So it's not that this is a benign disease, but the follow-up remains very short. And when you look at the ATLAS trial, despite its limitations, as sort of commented, the bar, when you look at beyond 3 months -- and maybe that's too high of a bar -- there's this exact same number of TURBTs in both groups.

So, to me, I think without that randomization, if you have new drug X, Y, or Z, or even more concerning to me is if you've got a doublet added on top of this and the bar is simply 3-month response when this has toxicity, if you read the paper on the PROs -- and you guys can go to that Journal of Urology paper -- there are patients that wanted to drop out of the trial. There were patients with severe pain. There were patients who couldn't work. Obviously, that's not

representative. We've heard some patients that had great responses; that it was a piece of cake to go through.

So I think randomization and randomized trials are the gold standard, not simply out of historical precedent. I think they're necessary. This is a common disease. They basically conducted a randomized trial, so I'll give the sponsor actually great credit. While it's imperfect, they did a randomized trial. There is evidence from it.

Anything else? Dr. Frenkl?

DR. FRENKL: Hi. Tara Frenkl, industry representative. I just want to agree with my urology colleagues and the patient a little bit more. Again, with everyone else, randomized controlled trials are absolutely the best, gold standard, but I do think that we should leave it a little bit open for the individual treatment that's being tested.

Like we saw some of the issues with coming to agreement with what would be an appropriate primary endpoint when comparing a medication to a

surgical procedure, it's not necessarily so straightforward, or maybe with equipoise for the patients as well in terms of their autonomy and deciding which treatment they would necessarily go for. I just think it's not so straightforward that we can demand a randomized controlled trial in every situation.

DR. PAZDUR: Since that was the industry's perspective, let me give you the regulatory perspective.

DR. SPRATT: Dr. Pazdur?

DR. PAZDUR: Yes. If we don't require something, nobody will do it. Let's just be quite honest with you. Let us just be quite honest with you. If you say that a single-arm trial suffices, guess what? Nobody's going to do a randomized trial.

So that's why we're asking this question, really, to get some context around it and some strength from the committee as we go forward. And here again, this has nothing to do with this application. It does provide us -- if this drug is

approved -- a new standard, so to speak, where others can compare themselves to this, either in a superiority or potentially in a non-inferiority if we have the requisite information available to determine margins, et cetera.

So this is where our dilemma is. If we don't really require something, it goes to the lowest denominator here, not the highest denominator, for companies.

DR. SPRATT: Thank you.

This is Dan Spratt, UH Seidman, Case Western. What I'll say, and I'll use this opportunity, is while it's regulated differently, devices, such as surgery, in my opinion as a radiation oncologist where our devices are regulated not through this aspect of the FDA, I think that the bar is unbelievably low for devices used in oncology. What this is, is this is a surgery versus a drug, and as new devices are trying to get approved, I think it is absolutely astonishing to me that we do not hold them to a bar of clinical benefit. So that's my soapbox as

getting to be the chair.

DR. PAZDUR: Can I give you a regulatory perspective on that? Different laws and different regulations.

DR. SPRATT: Yes. Understood. But it's a cancer therapy, which shouldn't be so weird to compare a drug and the device if they're cancer therapies.

Any other discussions on this?

(No response.)

DR. SPRATT: Okay.

We will now proceed to question 2, which is a -- oh. I'm sorry. I need to provide a summary of the first point.

The discussion points raised is that one of the key things that's hanging up probably many of the people is the word "required." I think that everyone pretty much said they either favor or acknowledge the strengths of randomized trials. They would be nice if they can be conducted. It ranged from that to that they should definitely be required.

I think that there are potentially instances, especially if there are concerns of feasibility, to use this word "required" is of concern. And from the FDA, the point that if it's not required, it just simply may not, or will not, be done.

Anything else?

Yes? From the FDA.

DR. SUZMAN: Daniel Suzman, FDA. I just wanted to pose a question to Dr. Garraway and Dr. Ball. Do you have any concerns around the feasibility of future randomized trials in this setting? Would you have concerns around randomization to, let's say, TURBT versus a novel drug therapy?

DR. BALL: Mark Ball, National Cancer Institute. I don't have concerns. I mean, this is a common disease state where we do have a standard of care that's been used for a long time, so I don't have concerns.

DR. GARRAWAY: Yes. I agree that I don't necessarily have concerns about the feasibility. I

guess my only concern, as has been mentioned earlier, is that this is a really heterogeneous disease, so how are you really going to make it so you're comparing apples to apples? I think that's one of the issues here, is how do you distinguish, in this case, an effect of the medication versus the natural history of the disease when the natural history of the disease is so variable?

So I guess that's the only thing. I think maybe more careful design when thinking about that, when you have such a spectrum in terms of how patients recur and respond.

DR. SUZMAN: Great. Thank you.

DR. SPRATT: So to summarize part 2, doing a randomized trial is feasible; minimal concerns. If anything, probably some caution or attention to the enrollment criteria to make sure that it's at least a reasonably homogeneous population knowing it may be challenging. And I will just add, kudos to the sponsor. They conducted a randomized trial, so kudos to them.

We'll now proceed to question 2, which is a

voting question. We'll be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing. They'll continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to. We will continue in the same manner until all questions have been answered or discussed.

For question 2, is the overall benefit-risk of the investigational therapy UGN-102 favorable in patients with recurrent low-grade intermediate-risk

non-muscle invasive bladder cancer?

Are there any questions about the wording of this?

(No response.)

DR. SPRATT: Not hearing any, give us one moment. We're going to make sure the voting systems are in front of who it needs to be in front of. We may do a little musical chairs. Hold on.

(Pause.)

DR. SPRATT: Excellent. We solved the problem.

If there are no further questions or comments concerning the wording of the question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection, the light may continue to flash. If you were unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. SEO: This is Jessica Seo, DFO. The results for question 2 are as follows: 4 yeses, 5 nos, and 0 abstentions.

Dr. Spratt?

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

We will begin with Ms. Johnston.

MS. JOHNSTON: I voted yes. I vote yes as the representative of the patient and caregiver population. I feel the way that the risk-benefit ratio was expressed in this question, this is the best representation of this population.

DR. SPRATT: Dr. Gradishar?

DR. GRADISHAR: Bill Gradishar, Northwestern. I voted yes, the rationale being that although I think everybody articulated clearly that the data sets may have been less than perfect to answer the question, my overall impression was

that for this population, the risk-benefit ratio still favored this as an option for patients.

DR. VASAN: Neil Vasan. I voted no. I was really thinking about benefit and risk. I felt that the risk was actually lower and harder to compare it with apples and oranges because these are different procedures, but that the benefit was very hard to ascertain given the wide heterogeneity. I also think that this was a missed opportunity to run a randomized controlled trial given the frequency of the disease and the commonness of the procedure.

DR. SPRATT: Dan Spratt. I voted no, and I'll list the reasons why. I think without the full randomized trial -- but again, I do want to commend and give kudos to the applicant for showing it's feasible to conduct a randomized trial -- it's very hard to determine the true benefit of this.

I also will say I struggle; that while I understand from the experts in this field that a 3-month complete response is kind of a standard in this field, that is for an indolent disease a

unbelievably short-term endpoint, to me, to demonstrate clinical benefit. There's very limited long-term follow-up. This was achieved 75 percent plus or minus the time.

Again, I realize the differences in the FDA's analysis and the applicant's analysis, but when you look across these trials, in ENVISION, about half of patients by 18 months, by the FDA's analysis, who had a CR initially were still in CR; in the OPTIMA II trial, 57 percent of patients progressed at 9 months after a CR at 3 months; and in ATLAS, 60 percent progressed at 12 months after a CR at 3 months; again, using the FDA's analysis, the applicant's would be higher rates.

The follow-up, to me, is far too short in this indolent disease process to know how this will impact subsequent salvage therapies. This does increase toxicity. It's not that there's no toxicity. The whole point of this should be to delay TURBT not for the sake of TURBT but to improve quality of life. That was not demonstrated convincingly. And then as we've talked before,

after 3 months, there were similar rates of TURBT in the ATLAS trial, and as we've talked about, the control arm may be inadequate.

The thing that the FDA won't use, but we can discuss, is in the editorial to the ATLAS trial, the financial toxicity, the BCAN representative from the foundation that this is a $140,000 treatment for something that won't change how many TURBTs you need after 3 months. Patients need to realize, outside of a trial going to these populations, we're talking about that's something real and impactful to them.

So this is why I voted no. And especially it did not change or reduce the need for cystectomy, conversion to muscle invasive disease, and, of course, endpoints which would be unlikely to achieve such as metastasis or death, so I voted no.

DR. CONAWAY: Mark Conaway. I also voted no, and I agree completely with reasons from Drs. Vasan and Spratt as to why they voted no. So I voted no despite the compelling testimony in the

open public hearing. I think, bottom line, for me, there were just too many uncertainties about the actual levels of benefit and risk for me to say it was favorable.

DR. MADAN: Ravi Madan, National Cancer Institute. I voted no. I think the sponsor makes a very compelling case for the need for therapies in this disease state. That makes me optimistic that randomized controlled trials could be done to really get to the heart of the questions here.

I'm pleased that a lot of the toxicity is low grade, but that's still toxicity, and the benefits here, for me, are really hard to define in a population that is heterogeneous and has the potential for indolent disease state. So that was why I voted no. Thank you.

DR. McKEAN: Heidi McKean. I voted no. I understand that CR is a reflection of drug effectiveness, and duration of a response can be effectiveness of the drug or the natural history of disease. And in this population, a randomized controlled trial is feasible and would have really

helped us understand the clinical meaningfulness of the intervention.

DR. BALL: Mark Ball, National Cancer Institute. I voted yes. I would like to acknowledge that a fully-enrolled randomized clinical trial would have mitigated many of the critiques, and I think that would have made the sponsor's case a lot stronger today.

Regardless though, I think that even the demonstrated efficacy at 3 months, a reflection of a non-surgical intervention to treat this disease state, is encouraging, and that the signal at 12 months and beyond, even though there are differences in the interpretation of the data, is quite encouraging.

Finally, I think the toxicity profile presented to me is not alarming, and I think, as someone who sees these patients, there's broad overlap with this toxicity profile, and also the toxicity of untreated bladder cancer, and the toxicity of TURBT. It is hard to suss out those differences in this data, but I don't find the

toxicity profile alarming and, therefore, the benefit-risk ratio favorable. Thank you.

DR. GARRAWAY: Isla Garraway, urology, UCLA. I voted yes because, number one, this is a very important option for select patients who have significant comorbidity and they're not ideal surgical candidates. Anytime you can delay surgery or prevent surgery, it's a win for everyone, especially given the fact that OR time is a limited resource as well, and this is usually an indolent disease in the majority of patients.

I agree with my colleague, Dr. Ball, that the toxicities in this case that were reported are very difficult to compare out of context since the study design was not really meant to compare to the toxicities that happen with TURBT. And just in general, patients in this age group oftentimes develop urinary symptoms regardless, so I think it's hard to really put that into complete context. I think the drug is safe and is promising for delaying and avoiding TURBT.

DR. SPRATT: Before we adjourn the morning

session, are there any last comments from the FDA?

DR. PAZDUR: Just to thank everybody for a very productive discussion. Personally, I consider this a relatively split vote, so we will be meeting with the sponsor to look at future directions. Thank you.

Adjournment

DR. SPRATT: Thank you.

We'll now adjourn the morning session and break for lunch. We will reconvene at 1:00 pm Eastern Time. Panel members, please remember that there should be no chatting or discussion of the meeting topics during the break amongst yourselves or with any member of the audience. Additionally, you should plan to reconvene here at 12:50 Eastern Time to ensure you are seated before we reconvene at 1:00 pm. Thank you so much.

(Whereupon, at 11:23 a.m., the morning session was adjourned.)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Afternoon Session

Wednesday, May 21, 2025

1:00 p.m. to 4:39 p.m.

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P R O C E E D I N G S

(1:00 p.m.)

Call to Order

Introduction of Committee

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

My name is Dr. Daniel Spratt, and I'll be chairing this meeting. I now call the afternoon session of day 2 of the May 20 to 21, 2025 meeting of the Oncology Drugs Advisory Committee to order. We'll start by going around the table and introducing ourselves by stating our names and affiliations. We'll start with the FDA to my left and go around the table.

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

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

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

DR. FALLAH: Jaleh Fallah, Clinical Reviewer, Division of Oncology 1, FDA.

DR. MAGUIRE: Will Maguire, Clinical Reviewer, Division of Oncology 1, FDA.

DR. GRADISHAR: Bill Gradishar, breast medical oncologist, Northwestern University.

DR. VASAN: Neil Vasan, breast oncologist and physician scientist, NYU Langone.

DR. SEO: Jessica Seo, Designated Federal Officer, FDA.

DR. SPRATT: Dan Spratt, Chair of Radiation Oncology at UH Seidman Cancer Center, Case Western Reserve University.

MR. KUNGEL: Terry Kungel. I've been the Chair and CEO of the Maine Coalition to Fight Prostate Cancer for about 15 years. And I just want to say that when you look at the history of

prostate cancer, it's been amazing to see the new drugs come along. And one of the things that I don't think the patient community does enough for the FDA or the applicant is to say thank you for all the new treatments that have come along.

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

DR. MADAN: Ravi Madan, medical oncology, National Cancer Institute.

DR. McKEAN: Heidi McKean, community medical oncologist, Avera Cancer Institute.

DR. GRAFF: Julie Graff, prostate cancer, clinical medicine, and also work at the VA Portland and run a clinical trials consortium. Thank you.

DR. TENDLER: Craig Tendler, former Global Head of Oncology Clinical Development and Medical Affairs at Johnson & Johnson, and now an independent consultant and industry representative for this ODAC.

DR. SPRATT: Thank you.

For topics such as those being discussed at this meeting, there are often a variety of

opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in their Sunshine Act, we ask that the advisory committee members take care that their conversations about the topics 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 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. We'll leave it at that. We're not having another lunch. Thank you.

Dr. Seo will read the Conflict of Interest

Statement for the meeting.

Conflict of Interest Statement

DR. SEO: Thank you, Dr. Spratt.

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

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those 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 their 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 discussion of supplemental new drug application, or sNDA, 211651/S-013, for talazoparib, or trade name Talzenna, capsules, submitted by Pfizer, Incorporated. The proposed indication or use is in combination with enzalutamide for the treatment of adult patients with metastatic castration-resistant prostate cancer. This is a particular matters meeting during which specific matters related to Pfizer's sNDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, 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. Craig Tendler is participating in this meeting

as a non-voting industry representative, acting on behalf of regulated industry. Dr. Tendler's role at this meeting is to represent industry in general and not any particular company. Dr. Tendler is an independent pharmaceutical consultant.

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

Thank you, and I'll return the floor to you, Dr. Spratt.

DR. SPRATT: Thank you.

We will now proceed with the FDA opening remarks, starting with Dr. Jaleh Fallah. Thank you.

FDA Opening Remarks - Jaleh Fallah

DR. FALLAH: Good afternoon. My name is Jaleh Fallah. I'm a medical oncologist and the FDA's cross-disciplinary team lead for this application. Today, we will be discussing the expansion of the indication for use of talazoparib with enzalutamide from an indication that is currently limited to patients with HRR-mutated metastatic castration-resistant prostate cancer, or mCRPC, to a considerably broader indication in all patients with mCRPC without the need for determination of the status of HRR gene mutation in their tumor.

Non-clinical studies of prostate cancer suggest an increased anti-tumor effect when combining PARP inhibitors with androgen receptor pathway inhibitors, or ARPIs, especially in tumors with BRCA or other HRR gene mutations. In non-clinical studies of prostate cancer cells lacking HRR mutation, it appears that androgen receptor inhibition can suppress the expression of HRR genes, providing a rationale for further

evaluation of the combination of PARP inhibitors and ARPIs in clinical trials of patients without HRR gene mutation. Several clinical trials, including TALAPRO-2, have been conducted to assess the efficacy of this combination in patients with mCRPC.

In June 2023, the FDA approved talazoparib with enzalutamide for the first-line treatment of patients with mCRPC and HRR gene mutation. The approval was based on the results of TALAPRO-2, a randomized, double-blinded, placebo-controlled trial that randomly assigned over 1,000 patients with mCRPC, including 399 patients with an HRR gene mutation, to receive enzalutamide with either talazoparib or placebo.

A statistically significant improvement in rPFS by blinded independent central review was demonstrated in both the all-comers and the combined population with an HRR gene mutation. At the time of the initial review, the overall survival results were immature.

Despite a statistically significant rPFS

improvement in the all-comers cohort, it appeared that the results were primarily attributed to the treatment effect in patients with an HRR gene mutation. Thus, for patients without an HRR gene mutation, the FDA did not consider the magnitude of rPFS improvement clinically meaningful in the context of the high prevalence of the non-HRR population; the fact that talazoparib is an add-on to an effective therapy; the toxicity, including severe anemia and need for blood transfusion in approximately 40 percent of patients; as well as the limited follow-up of overall survival.

The approval was, therefore, limited to patients with mCRPC with an HRR gene mutation for whom there was a statistically significant and clinically meaningful improvement in rPFS and favorable OS results.

At the final OS analysis, TALAPRO-2 met the prespecified threshold for statistically significant superiority of OS with talazoparib in all-comers, and in December 2024, the applicant submitted a supplemental application, which

included the final OS results from TALAPRO-2 requesting the expansion of the indication for mCRPC from HRR mutated to all-comers.

As shown in these figures, the rPFS and OS results continue to demonstrate a larger treatment effect in the subgroup with an HRR gene mutation. Of note, OS results in the all-comers population is clearly attributed to the larger OS improvement in the HRR-mutated population as shown in the bottom left figure.

However, a very small proportion of patients with an HRR gene mutation on the control arm received the subsequent PARP inhibitor after disease progression, a setting in which olaparib monotherapy has demonstrated a survival benefit, and thus the OS improvement for the HRR mutated in all-comers population in TALAPRO-2 may not be redemonstrated if the trial were conducted, according to the current clinical practice in the United States.

The FDA team is presenting this application today for the following issues: lack of

prespecified formal statistical testing of the non-HRR population and lack of support from prior trials of PARP inhibitors for approval in the non-HRR population.

The design of TALAPRO-2 was such that a large treatment effect in the HRR-mutated population could result in statistical significance in the all-comers population despite a much smaller or even no treatment effect in the non-HRR population.

Knowing the importance of HRR mutation as a predictive biomarker, the applicant also defined an additional formally tested cohort in TALAPRO-2 that included only patients with an HRR mutation. This would increase the likelihood of getting an approval for HRR-mutated mCRPC if the trial did not meet its primary endpoint in all-comers. However, the TALAPRO-2 design did not prespecify formal statistical testing for evaluation of efficacy in the population without an HRR gene mutation.

As a reminder, over 70 percent of patients with mCRPC do not have an HRR gene mutation. An

enrollment of an adequate number of patients, and enrollment of an adequate number of patients with non-HRR tumor for a formal statistical analysis is feasible for such a large patient population. In the absence of formal statistical testing, including a plan to control for false positive conclusions, it is challenging to determine whether there is truly a treatment effect in the non-HRR population, and any apparent effect in these exploratory analyses may just be due to chance.

If the proposed all-comers indication were approved, it would be the first approval of a PARP inhibitor for the treatment of a biomarker on selected prostate cancer population. Results from previous trials of PARP inhibitors in patients with mCRPC have demonstrated futility or unfavorable results in the non-HRR population. The lack of support for the exploratory results in the non-HRR population in TALAPRO-2 from other trials of PARP inhibitors further raises our concern that any apparent efficacy in the non-HRR population in this trial may just be due to chance.

The applicant has provided non-clinical data that talazoparib may be differentiated from other PARP inhibitors due to differences in the mechanism of action; however, the adequacy of these data to consider the results of TALAPRO-2 entirely separately from trials of other PARP inhibitors is unclear.

The FDA considers these non-clinical data to be hypothesis generating and to serve as a reasonable rationale for conducting clinical trials of the combination of talazoparib with enzalutamide in patients with non-HRR-mutated mCRPC; however, any claims of differential efficacy for talazoparib compared to other PARP inhibitors cannot be proven in the absence of head-to-head randomized comparisons.

Additionally, the FDA notes that non-clinical data cannot be used as a replacement for clinical trials, and ultimately data from randomized clinical trials are required to determine the efficacy and safety in this population.

In summary, TALAPRO-2 demonstrated a statistically significant improvement in rPFS and OS in the all-comers population with mCRPC; however, the subgroup analysis by HRR status shows a larger treatment effect in patients with an HRR gene mutation.

Additionally, the OS improvement in the all-comers population was largely attributed to the OS results in the subgroup with an HRR mutation in which a very small number of patients on the control arm received subsequent therapy with a PARP inhibitor after disease progression, and the observed OS improvement may not be redemonstrated if patients with HRR-mutated tumor received a PARP inhibitor after disease progression. Therefore, the FDA considers the OS results in the all-comers population in TALAPRO-2 to be potentially misleading and not directly applicable to the non-HRR population.

Although the applicant was aware of the importance of HRR gene mutation as a predictive biomarker of efficacy from PARP inhibitors, there

was no plan for a prespecified formal analysis of efficacy in the non-HRR population in TALAPRO-2, leading to uncertainty in the benefit-risk evaluation of the results in this large patient population. Additionally, lack of supportive data from other trials of PARP inhibitors in this setting has further increased our concern that the results of the exploratory analyses of the non-HRR population in TALAPRO-2 may be due to chance.

We remind the audience that over 70 percent of patients with mCRPC do not have an HRR-mutated tumor. If we extend the indication, this will expose a large number of patients to the toxicities of the add-on drug for approximately 2 years in the absence of any substantial efficacy.

The prevalence of the biomarker-negative population should be taken into consideration when designing clinical trials of therapeutics with a predictive biomarker. When the prevalence of the biomarker-negative population is large enough to make a separate analysis feasible, the treatment effect in biomarker-positive and biomarker-negative

populations should be assessed separately with prespecified formal statistical analyses for adequate control of type 1 error in each biomarker-defined population.

Another important consideration is the adequate prospective determination of the biomarker status, as the inclusion of patients with unknown biomarker status makes the results in biomarker subgroups difficult to interpret.

The FDA believes that to best serve patients and the oncology community, more thoughtful trial designs are necessary when there is a known predictive biomarker. Granting an approval for a large biomarker-negative population despite an inadequate trial design rewards inadequate methodology and sends the wrong message by promoting flawed practices.

This topic was previously discussed at the ODAC meeting in April 2023 in relation to the PROpel trial of olaparib with abiraterone in this same mCRPC population. PROpel, similar to TALAPRO-2, did not formally evaluate efficacy in

the biomarker-negative population. Noting the importance of precision medicine, the advisory committee voted that the indication for the combination of olaparib with abiraterone should be restricted to BRCA-mutated population.

With these considerations in mind, we are asking the advisory committee to discuss the following topic that may apply both to this particular disease setting, as well as more broadly across tumor types. Discuss whether efficacy should be formally evaluated in a biomarker-negative population when the biomarker is predictive of response and the prevalence of the biomarker-negative group is high.

We also have the following question for discussion and voting by the advisory committee members. Are the TALAPRO-2 results sufficient to conclude a favorable benefit-risk profile for adding talazoparib to enzalutamide in patients with non-HRR-mutated mCRPC?

Thank you for your attention. Now, I'll turn it over to the chair.

DR. SPRATT: Thank you, Dr. Fallah.

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

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

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

speaking.

We will now proceed with the presentations from Pfizer.

Applicant Presentation - Johanna Bendell

DR. BENDELL: Good afternoon, Dr. Spratt, members of the Oncologic Drugs Advisory Committee, members of the FDA, and the public gathered here today. My name is Johanna Bendell, and before joining industry, I was a practicing medical oncologist and clinical investigator for over 20 years, and I'm now continuing my focus on improving the lives of cancer patients as Chief Development Officer at Pfizer Oncology.

I really appreciate your time today to review the data from the TALAPRO-2 study, supporting the use of talazoparib in combination with enzalutamide in patients with metastatic castrate-resistant prostate cancer unselected for HRR gene alterations.

The combination of Talzenna and enzalutamide is currently approved for the treatment of adult patients with HRR gene mutated mCRPC. This

indication was granted in June of 2023 based on the results of the radiographic progression-free survival primary analysis. These results were further confirmed by updated rPFS and final overall survival after two additional years of follow-up. In this population, we now observe a 53 percent reduction in the risk of progression or death and a 38 percent reduction in the risk of death.

Under review today is the proposed indication for patients with mCRPC who are unselected for HRR gene alterations. Today, we're going to present data supporting this indication from the unselected cohort of the TALAPRO-2 study, and we will address the key efficacy and safety questions that have been raised by the FDA.

Following this introduction, Dr. Pedro Barata from University Hospital Seidman Cancer Center will discuss the background and unmet need for patients with mCRPC. Dr. Dana Kennedy, Pfizer Oncology GU Development Head, will then present the efficacy and safety results. And finally, Dr. Neeraj Agarwal from the University of Utah

Huntsman Cancer Institute will discuss his clinical perspective on treating patients with mCRPC before I come back to provide the concluding remarks. Dr. Alicia Morgans from Harvard Medical School and Dana-Farber Cancer Institute is also available today to answer questions.

Today, you're going to be asked to consider why this particular combination has shown benefit where others have failed. As you've heard from the FDA, non-clinical studies have provided rationale for the evaluation of PARP inhibitors and androgen receptor inhibitors in clinical trials for patients with and without HRRm mutations.

We will demonstrate how the unique characteristics of talazoparib, as the most potent PARP trapper, and enzalutamide, as a direct AR signaling inhibitor and the only AR antagonist, are the key differentiators for this combination. The benefit of these differentiators is proven in the clinical efficacy for this combination in patients with unselected mCRPC.

Dr. Kennedy will describe the TALAPRO-2

study design and present the efficacy and safety data. TALAPRO-2 was prospectively designed to test the efficacy and safety of this combination in an unselected patient population based on the best available evidence at that time. This includes the mechanistic rationale, as well as clinical data that was published in 2018 that suggested similar efficacy between the biomarker positive and negative subgroups.

The study design was discussed with the FDA prior to initiation of the trial in 2019, including key elements of the population, endpoints, and statistical design of the two cohorts, unselected and HRR mutated selected. HRRm status in the study was well defined. Tissue NGS testing was used prospectively.

During the conduct of the study, ctDNA analysis became available, and we agreed with the FDA to retrospectively test additional baseline samples to increase our confidence in the definition of our patient population. This ultimately reduced the proportion of patients with

an unknown HRR status to approximately 5 percent.

Dr. Kennedy will also show you the unprecedented efficacy observed in the unselected patient population. TALAPRO-2 met its primary endpoint with statistically significant and clinically meaningful improvement in rPFS of over a year. We know that living longer without a progression is meaningful and important for our patients, and after more than 4 years of median follow-up, there was a statistically significant improvement in overall survival. We observed a 20 percent reduction in the risk of death against the active control of enzalutamide and a median survival of 45.8 months with a combination.

Of particular interest today is the subgroup of non-HRRm patients. This stratified, prospectively designed subgroup analysis demonstrated a meaningful improvement in rPFS. This rPFS difference is unlikely to be observed by chance given, first, the consistency across sensitivity analyses in the non-HRRm population; second, the improvement across multiple efficacy

endpoints; and third, the consistency of treatment effect in the combination arm in the ITT population. It is also reassuring that OS difference in the prospectively defined non-HRRm subgroup, although small, demonstrates a numeric trend in favor of the combination with no survival detriment.

Though the magnitude of benefit is greater in patients in the biomarker-positive subgroup, we importantly note that both biomarker positive and negative patients showed a benefit in clinical outcomes in this trial.

Through the course of our presentation, we will demonstrate the favorable benefit-risk assessment of talazoparib and enzalutamide treatment in the non-HRRm subgroup. This supports the proposed indication in patients with unselected mCRPC. We will show that outcomes remain poor in patients without HRR gene alterations and new therapies are needed to improve their survival.

There's a well-documented scientific rationale for the differentiated MOA of this

combination in patients with unselected mCRPC. The efficacy results seen in the non-HRRm subgroup of TALAPRO-2 are clinically meaningful and reflect a true treatment effect that is unlikely due to chance. And finally, the combination treatment results in more adverse events, most commonly anemia, which is generally well managed with dose modifications.

From the patient's perspective, as assessed by the patient-reported quality-of-life measurements in this trial, there were no clinically meaningful differences between treatment arms in global health status or quality of life. Taken together, the sum of the evidence demonstrates a favorable benefit-risk profile in unselected mCRPC patient population.

Now, I will hand over the presentation to Dr. Barata.

Applicant Presentation - Pedro Barata

DR. BARATA: Thank you, Dr. Bendell.

Good afternoon. I'm Pedro Barata. I'm a GU medical oncologist and Associate Professor of

Medicine at Case Western Reserve University, University Hospitals, Cleveland, Ohio. I have been compensated for participating in today's meeting; however, I have no financial interest in the outcome of the discussions today.

Metastatic castration-resistant prostate cancer, mCRPC, is an aggressive and rapidly progressive disease. We know the most common site of metastasis is to the bone, making biopsy sampling challenging. These patients experience urinary incontinence; decrease libido; bone pain; weight loss; weakness and fatigue, often due to baseline anemia and low testosterone. Their physical and mental health morbidity, along with quality of life, also declines rapidly over time. Unfortunately, their probability of being alive at 5 years is less than 40 percent. So for this fatal disease, our priorities are to delay disease progression and associated symptoms, maintain quality of life, and prolong survival.

Now, we understand that not all tumors are the same from the molecular point of view. Up to

30 percent of patients will harbor homologous recombination repair HR defects, while other tumors will have different alterations. Given the value of these biomarkers, it is critically important to implement molecular testing in clinical practice. And while molecular testing rates are increasing over time, today, less than 50 percent of patients in the U.S. are offered testing, or testing happens late, preventing them from benefiting from biomarkers-based therapies. Because the majority of first-line patients have no test results, or negative test results, androgen receptor pathway inhibitors, or ARPIs, such as enzalutamide or abiraterone are the most common initial treatments.

For a variety of reasons, including death, disease progression, comorbidities, and decreased performance status, less than 50 percent of patients end up receiving more than one line of systemic therapy. Further, as their clinical status deteriorates, they lose the opportunity to fully benefit from subsequent therapies. This helps address FDA's comment regarding the use of

subsequent PARP inhibitors in the TALAPRO-2 trial. It's not surprising given the poor prognosis of patients with HR gene alterations.

As an example, think of Dr. Maha Hussain, the BRCAAway trial, an academic endeavor in which crossover was prespecified. And still in that trial, less than 50 percent of patients went on to receive subsequent PARP inhibitors. So, our first chance to treat these patients is our actually best chance to improve their outcomes.

The median overall survival for mCRPC patients treated with ARPIs is less than 3 years from the time of diagnosis. This actually has not improved in over a decade, even in contemporary clinical trials; and, actually, real-world evidence is even worse, more like 24 to 30 months. Clearly, we've got to do better. We can do that by building on the ARPI backbone with rational drug combinations such as those with PARP inhibitors.

Monotherapy PARP inhibitors are well proven to benefit patients with HR mutations, but how can the combination of PARP inhibitors with ARPIs

benefit patients with and without HR mutations?

First, as you can see here in the figure on the left, when androgen receptor gene expression is inhibited in the prostate cancer cell line, HR gene expression is also decreased. So ARPIs like enzalutamide can decrease HR function, even in tumors without a specific HR mutation, resulting in an increased sensitivity to PARP inhibitors like talazoparib.

Secondly, inhibition of PARP decreases the androgen receptor activity, as shown by the in vitro data here in the center, inhibiting PARP with talazoparib, and therefore can increase the sensitivity with an ARPI like enzalutamide. And finally, shown on the right, we see that the combination of enzalutamide with PARP inhibition is better at slowing tumor growth compared to either agent alone, illustrating the crosstalk between these two pathways and the potential for these combinations to benefit patients with and without HR mutations.

The data supporting this rationale has

actually been generated for over a decade from many labs around the world using a variety of scientific methods and preclinical models, and are broadly published in the scientific literature. From the early work, Dr. Karen Knudsen's lab identified the interaction between HR and AR pathways, to a detailed molecular analysis showing association of the AR pathway activity with HR gene expression in human prostate cancer tissue, to a variety of in vivo work showing efficacy of combining enzalutamide and other androgen receptor inhibitors with PARP inhibition in HR-proficient animal models.

Just as an example, in an AACR meeting just a few weeks ago, data from Dr. Shafi's lab showed histone acetyltransferase, CBP 300, which acts as an androgen receptor co-activator, regulates DNA repair, particularly homologous recombination, and the inhibition of this protein plus PARP inhibition enhanced the efficacy in non-clinical models, as well as patient-derived explants. So in summary, there is a substantial body of evidence supporting

the logic of the combination and the opportunity it may provide to mCRPC patients, even those without HR alterations.

In conclusion, overall survival for unselected patients with mCRPC has remained below the 3-year mark for over a decade, and our patients do need progress. Optimal first-line therapy is our best opportunity, and in many cases, the only chance to improve those outcomes for mCRPC patients.

Enzalutamide is a backbone for metastatic prostate cancer treatment, and it has a well-understood safety profile. There is strong biological rationale for the combination of enzalutamide with talazoparib for patients with and without HR mutations due to the mechanism of action and the crosstalk between the two pathways. So importantly, this combination has the potential to provide a meaningful breakthrough for our mCRPC patients.

Thank you very much. Dr. Kennedy will now present efficacy and safety data from the

talazoparib trial. Thank you.

Applicant Presentation - Dana Kennedy

DR. KENNEDY: Thank you, Dr. Barata, and good afternoon. I'm Dana Kennedy, GU Development Head at Pfizer Oncology. I'm going to share the key efficacy and safety data for talazoparib and enzalutamide in patients with mCRPC unselected for HR gene alterations.

TALAPRO-2 is a robustly designed pivotal, double-blinded, phase 3 trial. It was conducted in two cohorts, Cohort 1, the unselected population, and Cohort 2, the HRRm selected population. Patients were stratified by prior abiraterone or docetaxel given for castrate-sensitive disease, and importantly, they were prospectively stratified by HRR gene alteration status, either deficient versus non-deficient or unknown.

Patients were randomized 1 to 1 to talazoparib and enzalutamide or placebo and enzalutamide. After Cohort 1 completed recruitment, Cohort 2 went on to enroll only patients with HRR gene alterations. Ultimately,

805 patients were enrolled to Cohort 1, 399 patients were enrolled to Cohort 2, and there were 169 patients with HR gene alterations that were common to both cohorts.

The primary endpoint was rPFS by blinded independent central review, and overall survival was the key alpha-protected secondary endpoint. The alpha for the independent primary endpoint of radiographic progression-free survival was split equally between the unselected and HRRm selected cohorts, with overall survival as the key alpha-protected secondary endpoint in each cohort. As highlighted by Dr. Bendell, given the best science and clinical data in 2018, suggesting similar efficacy in biomarker positive and negative populations, we did not alpha control the non-HRRm subgroup in the unselected cohort.

At data cutoff 1 in August of 2022, rPFS was positive in the unselected cohort, and an interim analysis of survival favored the combination but was immature. At data cutoff 2 in October of 2022, the interim rPFS efficacy threshold was crossed and

became the final rPFS analysis in Cohort 2, which was positive. The interim survival analysis remained immature. At data cutoff 4 in September of last year, the final overall survival analysis in both cohorts was positive.

Turning our attention to the unselected population, the focus of the proposed indication, the primary rPFS results demonstrated a 37 percent reduction in the risk of progression or death. With an additional 2 years of follow-up, we observed a sustained rPFS benefit with a hazard ratio of 0.667. The median rPFS of talazoparib and enzalutamide has now been reached at 33.1 months, which is over a year improvement compared with enzalutamide alone.

Updated subgroup analysis of rPFS demonstrated a highly consistent treatment effect in favor of talazoparib and enzalutamide. This favorable treatment effect was consistent across relevant clinical subgroups such as age, ECOG performance status, Gleason score, stage of diagnosis, and prior taxane or abiraterone.

Importantly, the stratified subgroups of HR-deficient versus non-HR deficient or unknown, highlighted here in green, also demonstrated rPFS benefit in favor of the combination.

At the final analysis, there is a statistically significant and clinically meaningful improvement in overall survival, with a 20 percent reduction in the risk of death and a median overall survival of 45.8 months with the combination versus 37 months with enzalutamide alone, an improvement of almost 9 months in median survival over an active control.

Subgroup analysis of overall survival also demonstrated a consistent treatment effect in favor of talazoparib and enzalutamide. The favorable treatment effect of the combination was observed across all clinically relevant subgroups, including the stratified subgroups of HR status and prior taxane or abiraterone. The observed hazard ratios fall within the 95 percent confidence interval of the ITT population, as shown here in gray, although the upper bounds do cross 1 for several clinical

subgroups.

The treatment effect was also consistently maintained across secondary endpoints. We see improvements in PSA 50 response, confirmed overall response rate, and a near doubling in the complete response rate. Time-to-event endpoints also favored the combination, including time to PSA progression, first subsequent therapy, first sight of toxic chemotherapy, and PFS2, where hazard ratios ranged from 0.57 to 0.79.

Turning our focus to the molecular subgroups, it's important to remember that all patients had prospective NGS testing of tumor tissue, and approximately 6 percent also had prospective ctDNA testing that informed their HRR status. This prospectively assessed status was used for stratification, which is the strength of the TALAPRO-2 study design.

As shown on the left, approximately 20 percent of patients had detectable HRR gene alterations and 80 percent did not have alterations detected or were unknown. Unknown status was

almost exclusively based on tissue results and represented about 30 percent of the population. This is consistent with the known performance of the foundation medicine assay, and this is why we collected additional baseline samples for retrospective ctDNA testing to resolve the anticipated unknowns.

In the non-HRRm unknown subgroup, the hazard ratio for rPFS was 0.739 with a median improvement of 10.9 months, consistent with the results in the ITT population. There's a numeric trend in overall survival in favor of the combination with a hazard ratio of 0.878 and no indication of survival detriments.

To better isolate the efficacy in the non-HRRm population, we agreed with the agency to conduct a stringent assessment of all baseline tumor and ctDNA samples. In this assessment, the HRRm population, the 33 percent shown in blue, was defined by the presence of an alteration in either test. A more stringent definition requiring both ctDNA and tissue to be negative was used to define

the non-HRRm population, the 39 percent shown in dark gray. This population has the highest certainty for not having an HRR gene alteration.

The remaining group are those with one negative test result and the other unknown, or both unknown, where there is less certainty regarding the detection of HRR gene alterations primarily by ctDNA. Those who are negative by one test is 23 percent, and those who are truly unknown is 5 percent of the population. Only 44 out of 805 patients enrolled.

In reality, patients either have an HRR gene alteration or they do not, regardless of the limitations in testing. We will focus on the patients with no HRR gene alteration detected by both tests as we seek to understand the translation of the preclinical hypothesis that talazoparib and enzalutamide may extend benefit to these patients.

In this exploratory subgroup analysis, where we have the highest certainty that HR gene alterations are not present, we observe a favorable treatment effect for rPFS with a hazard ratio of

0.757 and a median improvement of over 13 months. There is also a 22 percent reduction in the risk of death and a 9.2-month improvement in median survival, indicating no detriment in the non-HRRm population. Notably, these results are consistent with the ITT population.

The magnitude of progression-free survival gains are clinically important in this population without detectable HRR gene alterations, where a high unmet need exists for new therapies, and these results support the biologic rationale for activity in non-HRRm tumors.

We also see that the treatment effect favored the combination in this non-HRRm subgroup across secondary endpoints. There were numeric improvements in PSA 50 response, confirmed overall response rate, and a doubling of the confirmed CR rate, evidence of direct anti-tumor activity. Time to PSA progression, first subsequent therapy, and first cytotoxic chemotherapy, as well as PFS2, also favored the combination with hazard ratios ranging from 0.4 to 0.78.

Multiple definitions for non-HRRm will be presented today. Regardless of which definition is used, either protocol defined, the sponsor's, or FDA's exploratory definitions, we observe a consistent improvement across primary and secondary endpoints. This supports the overall treatment effects in this subgroup and is unlikely to be due to chance.

Now, when we look at the rPFS benefit across the ITT population, the HRRm, non-HRRm, the undetermined subgroup, we see consistent outcomes with hazard ratios ranging from 0.527 to 0.757. Finally, when we look at overall survival, we see a highly consistent gain in the medians across the ITT population, the HRRm, non-HRRm, and undetermined subgroups, at 45 to 46 months.

We see the difference in the hazard ratios driven by the variable performance of enzalutamide in the control arm, which on one hand reflects the poor prognosis in the HRRm population, and on the other hand reflects the better than expected performance of enzalutamide in the undetermined

subgroup. Treatment with the combination appears to negate the negative prognostic impact of an HR gene alteration, and thus provides all patients the opportunity for meaningful survival gains.

Notably, this is not a case where the results in one group are positive and the other are negative. Patients in both subgroups experience meaningful benefit.

In summary, TALAPRO-2 was a robustly designed pivotal study with a well-characterized patient population. The primary endpoint of progression-free survival was significantly prolonged, providing a median improvement of over a year. This is the first study in this indication to result in a clinically meaningful and statistically significant improvement in overall survival, with a 20 percent reduction in the risk of death compared to an active control.

We observed a favorable treatment effect in the most rigorously defined non-HRRm subgroup, and this effect is maintained across efficacy endpoints and is unlikely due to chance. The final efficacy

results of TALAPRO-2 demonstrate a meaningful treatment benefit for talazoparib and enzalutamide in a well-defined mCRPC population.

Now, moving on to clinical safety, with the combination, we observe a safety profile that is consistent with the known profile of each agent. The most common adverse event observed of talazoparib is anemia, which is on target, expected, and addressed in the current U.S. prescribing information. The most common adverse events associated with enzalutamide include musculoskeletal pain and fatigue.

With over 500 patients in the pooled safety database and an additional 2 years of follow-up, the safety profile has remained consistent with no new safety signals.

The median duration of follow-up in TALAPRO-2 was over 4 years, the longest of any contemporary study in mCRPC. Median duration of exposure was longer for both talazoparib and enzalutamide in the combination arm, suggesting that patients tolerated therapy well. Putting into

context that half of patients had a dose reduction of talazoparib, the median relative dose intensity remained high, over 80 percent. Importantly, we see that patients were able to stay on treatment with enzalutamide, a median of 7 months longer, enabling patients to benefit from enzalutamide longer when administered with talazoparib.

Overall, there were no meaningful safety differences between patients selected or unselected for HR gene alterations, so the results I will share with you today are from the unselected population.

More patients on the talazoparib arm experienced grade 3 or 4 adverse events, and there was a numerically lower rate of grade 5 events. Dosing interruptions and reductions were common in the talazoparib arm and were primarily related to anemia. With appropriate dose modifications, most patients were able to stay on treatment in the absence of progression, and there was a relatively low rate of discontinuations due to toxicity at about 22 percent.

Consistent with the known safety profile of talazoparib, the most common treatment-emergent adverse effects were hematologic: anemia, neutropenia, and to a lesser degree, thrombocytopenia and leukopenia. Anemia occurred in 68 percent of patients, with 45.7 percent experiencing grade 3 and 3.3 percent experiencing grade 4. The other hematologic toxicities were less frequent, with a low incidence of grade 3 or 4 events. The majority of other treatment-emergent adverse events were generally balanced between the treatment arms.

Anemia predominantly occurred early in the course of treatment. This plot shows the incidence of anemia over time, with all grades shown in black and grade 3-4 shown in green. The incidence peaks by week 13, and then declines, with relatively few new grade 3 or 4 events occurring after 40 weeks of treatment.

It's important to note that patients with a hemoglobin of greater than 9 were eligible for enrollment, and about half of patients in the

combination arm entered TALAPRO-2 with grade 1 or 2 anemia, reflective of a real-world population. Like anemia, the post-baseline decrease in hemoglobin occurred relatively early in treatment and nadired by week 13. We then observed increases over time that are within 1 gram per deciliter of baseline levels. In mirroring the rate of grade 3 anemia and post-baseline decline in hemoglobin, we also see the incidence of transfusions peaks by week 13 and then decreases to a low rate over time.

So how was anemia managed in the study? Nearly half of patients had an anemia-related dose interruption or reduction of talazoparib. As shown on the previous slides, these events tended to occur early in the course of treatment, and with appropriate intervention, including dose interruption, supportive care measures, including transfusion, and dose reduction, fewer than 10 percent of patients discontinued treatment with talazoparib due to anemia.

When we look at the safety results at the primary rPFS analysis and final OS analyses, we see

that the overall profile remains unchanged. The overall incidence and rate of grade 3 or 4 toxicities has remained consistent with an additional 2 years of follow-up.

We also see no clinically significant changes in the treatment-emergent adverse events of special interest at this final data cutoff. We observed one case each of AML and MDS at the primary rPFS analysis, and with an additional 2 years of follow-up, no new cases have been reported.

There were no clinically meaningful differences observed between treatment arms and patient-reported quality of life as measured by the EORTC QLQ-C30, a validated cancer-specific questionnaire. Assessments were administered frequently during the course of treatment until progression. All scales were scored from 0 to 100, with between group differences of 5 to 10 points considered clinically meaningful.

This plot shows the mean change from baseline in global health status and quality of

life at each on-treatment assessment in the first 2 years. Greater differences in quality of life appear to match the incidence of anemia occurring early in treatment. Overall, we did not observe a clinically meaningful difference between the treatment arms.

There were also no clinically meaningful differences between arms as seen in function and symptom scales with the EORTC QLQ-C30 assessment tool. Longitudinal mixed model effects showed no clinically meaningful differences between arms in all function and symptom scales, including global health status and quality of life; physical and role functioning; as well as fatigue, pain, and dyspnea.

We conducted exploratory analyses within the talazoparib arm to better understand quality of life in patients with and without grade 3-4 anemia. At week 13, a greater difference in global health status and quality of life was observed, which coincides with the nadir and hemoglobin levels. This difference improves over time as the frequency

of anemia declines. Global health status and quality-of-life scores otherwise appear similar throughout the study. These findings were also observed for function and symptom scales, including fatigue, physical, and role functioning.

In summary, the safety of the combination is consistent with the known profile of talazoparib and enzalutamide and remains unchanged with two additional years of follow-up. Anemia is the most common adverse event related to talazoparib. It occurs relatively early in the treatment course and is manageable with dose modifications and standard supportive care, including transfusions. The rates of anemia decrease over time, and the rate of discontinuations due to anemia is less than 10 percent.

Quality-of-life scores were generally similar among patients experiencing grade 3 and 4 anemia and those who did not. Importantly, patients were able to benefit from enzalutamide longer when administered with talazoparib, and there was no impact on the ability to receive

subsequent therapies. Overall, the safety profile of talazoparib and enzalutamide supports an acceptable benefit-risk assessment for the proposed indication.

I'll now turn it over to Dr. Agarwal to provide his clinical perspective.

Applicant Presentation - Neeraj Agarwal

DR. AGARWAL: Thank you, Dr. Kennedy, and good afternoon. I'm Dr. Neeraj Agarwal. I'm a Professor of Medicine and a GU medical oncologist and Presidential Endowed Chair of Cancer Research at the Huntsman Cancer Institute, University of Utah. I'm the principal investigator and the steering committee member of the TALAPRO-2 trial, and I have not received any financial compensation from the sponsor, and I have no conflict of interest financially.

As someone who has treated patients with this treatment, I would like to discuss my perspective on the use of this combination for patients with mCRPC.

One of your first questions, maybe, is why

is talazoparib and enzalutamide different from other PARP inhibitors and ARPI combinations that have failed to show statistically significant overall survival in unselected mCRPC patients?

The answer likely lies in key differences in the drugs themselves. Enzalutamide directly inhibits the androgen receptor, preventing it from binding to androgens and triggering cell growth. In contrast, abiraterone works more indirectly by inhibiting androgen biosynthesis, highlighting the clinical difference between these agents.

A real-world study of approximately 6,000 mCRPC patients in the U.S. VA hospital system showed a statistically significant improvement in overall survival with enzalutamide versus abiraterone. Talazoparib is differentiated within the PARP inhibitor class as the most potent PARP trapper. In combination with enzalutamide, this combination contributes to anti-tumor effects, even in HRR-proficient tumor cells.

Of the three most recent PARP inhibitor ARPI combination studies, TALAPRO-2, PROpel, and

MAGNITUDE, TALAPRO-2 is the only study that leveraged the most potent PARP trapper, talazoparib, with a direct and potent inhibitor of androgen receptor enzalutamide, and we see these key differences translate clinically.

Now, cross-trial comparisons should always be interpreted with caution, but when we look at TALAPRO-2 data, shown here in the blue, next to the PROpel data, shown in red, we see that in the unselected ITT population, talazoparib with enzalutamide has a longer rPFS and overall survival medians compared to olaparib in combination with abiraterone.

Importantly, we consistently see stronger results with talazoparib plus enzalutamide in key subgroups, including those negative for BRCA, by both tissue and ctDNA testing. These data show that unlike PROpel, TALAPRO-2 results were not driven by patients with BRCA mutations.

So how do the TALAPRO-2 data fit into the current landscape of first-line therapies for patients unselected for HRR mutations?

With a median rPFS of approximately 33 months and a median overall survival of approximately 46 months, we see that talazoparib plus enzalutamide has compelling efficacy among other first-line treatment options, which we can use today, including some from very contemporary clinical trials. As Dr. Barata described earlier, survival outcomes for patients without known predictive biomarker have been relatively stagnant for the last 10 years. Talazoparib plus enzalutamide therefore represents a meaningful breakthrough in the treatment of these patients.

So given these data, how would I use this combination in clinic?

At the time of metastatic prostate cancer diagnosis, guidelines recommend testing for HRR mutations. The patients in reality either have HRR mutations or do not have HRR mutations. Either way, TALAPRO-2 data showed improvement, as we can see here, in progression-free and overall survival that would be meaningful for my patients. And because we are already using this combination in

biomarker-selected patients, we know what side effects to expect and how to manage them.

As FDA has noted, the addition of talazoparib to enzalutamide increased hematologic toxicity. Anemia is the most frequent on-target side effect. In the TALAPRO-2 trial, approximately 50 percent of patients experienced grade 3 anemia. Please note that half of the patients in the talazoparib group had grade 1 or 2 anemia at baseline, which contributed to the frequency of grade 3 for anemia during the study.

In my experience, the protocol language requiring rapid resolution of anemia within 8 weeks was the biggest driver of transfusion. So if you could not correct the hemoglobin to above 9 gram percent within 8 weeks, the patient had to discontinue protocol treatment. And in that case, in many of these patients, we could only correct the hemoglobin level to above 9 gram percent by giving them blood transfusion. But in the regular clinic setting, we do not have such strict restrictions or protocol requirements and, hence,

transfusions in my clinic are rare with appropriate dose modifications.

Physicians that treat metastatic prostate cancer are well-versed in managing anemia. It is a common side effect within the first 3 months for many of the therapies we use today. It can be managed through monitoring routine blood tests, often locally, on a monthly basis and timely dose modifications per current talazoparib prescribing information.

The manageability of anemia is evident by the long treatment duration of talazoparib in the study of 19.7 months and the low rate of discontinuation due to anemia at 8 percent, and with no clinically meaningful difference in quality of life as reported by the patients. These data demonstrate, in my mind, an acceptable safety profile.

So how would I have a conversation with a patient without known HRR mutation status about the available treatment options?

This is a typical patient ready to start

treatment with an ARPI for a newly diagnosed mCRPC. Enzalutamide is a commonly utilized ARPI in this setting and delays disease progression by approximately 20 months. With one daily pill, my patient may gain an additional 11 to 14 months before disease progression. This could also mean in the context of castration-resistance setting, the lethal form of disease, delaying symptoms such as bone pain, fractures, and decreased quality of life. And now we have overall survival data showing an increase in survival of 9 to 12 months in different cohorts, as we have seen in Dr. Kennedy's talk, compared to enzalutamide alone.

This is an unprecedented survival benefit in the mCRPC setting. I would make my patients aware of the anemia risk, and you would manage this with routine blood tests, dose modifications, and supportive care as needed. I would also inform my patients of the potential for other more serious adverse events, although these occur rarely. Overall, talazoparib plus enzalutamide has a favorable risk-benefit profile for my patients with

and without HRR mutation. This life-prolonging therapy should be an option available to all patients with mCRPC and their physicians.

Thank you very much, and I will now hand the podium back over to Dr. Bendell for the closing remarks.

Applicant Presentation - Johanna Bendell

DR. BENDELL: Thank you, Dr. Agarwal.

As you've heard today, progress is needed to address the unmet need in patients with non-HRRm mutated mCRPC. The scientific rationale and the clinical data with talazoparib and enzalutamide set this combination apart from other PARP inhibitor and abiraterone combinations. The efficacy observed across endpoints in the non-HRRm subgroup represents a real treatment effect and not a chance finding.

Anemia is a frequent toxicity that occurs early in treatment and is manageable with routine monitoring, dose modifications, and supportive care, with patients able to stay on the combination for a median of 20 months.

With TALAPRO-2, we set out to evaluate the efficacy and safety of this combination in an unselected patient population. We observed statistically significant and clinically meaningful benefits in rPFS and OS for these patients. This is not a case in which the results in one group are positive and the other are negative. We see meaningful benefit in both HRRm and non-HRRm subgroups. Patients with and without HRR gene alterations will benefit from the approval of this combination.

Thank you so much for your time and consideration, and we look forward to your questions.

DR. SPRATT: Thank you so much.

Pfizer gets some brownie points for finishing early.

We will now proceed with the FDA's presentation, starting with Dr. William Maguire.

FDA Presentation - William Maguire

DR. MAGUIRE: Good afternoon. My name is Will Maguire, and I'm a medical oncologist at the

FDA. This supplemental new drug application, or sNDA for short, for talazoparib was submitted by Pfizer, 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 talazoparib in combination with enzalutamide is for treatment of adult patients with metastatic castration-resistant prostate cancer, briefly called mCRPC for the rest of this presentation. Talazoparib with enzalutamide is already approved for patients with homologous recombination repair mutated, or HRRm mCRPC; therefore, we consider the proposed indication to be essentially a new indication for patients without documented HRRm mCRPC.

We would like to ask the following question from ODAC. Are the TALAPRO-2 results sufficient to conclude a favorable benefit-risk profile for adding talazoparib to enzalutamide in patients with non-HRRm mCRPC?

To frame the discussion, this slide outlines why we have brought this application to ODAC. First, the TALAPRO-2 trial was suboptimal in that it did not formally evaluate the large subgroup of patients with biomarker-negative disease; therefore, there is uncertainty about the added effectiveness of talazoparib to enzalutamide in this subgroup.

Second, the proposed indication would be the first approval of a PARP inhibitor for unselected mCRPC. The chart shown here outlines the history of PARP inhibitor approvals for mCRPC. The initial approvals for PARP inhibitor monotherapy in later treatment lines are shown in the top two rows, and the more recent approvals in combination with androgen receptor pathway inhibitors, or ARPIs, for first-line mCRPC are shown in the bottom three rows.

In every approval so far, the indication has been restricted to patients with HRRm or BRCAm mCRP, consistent with broad acceptance in the field that these are predictive biomarkers for PARP

inhibition. To remind everyone, BRCA mutations are the largest subset of HRR mutations in prostate cancer and are thought to be the most sensitive of the HRR mutations to PARP inhibition.

A major risk of approving a drug in a large patient subgroup without proper evaluation is the risk of approving it in patients who will not receive benefit, and therefore who will experience unnecessary toxicity. As we will discuss, at least 70 percent of patients with mCRPC may possibly be affected by the decision to approve or not approve this sNDA. This would be the first approval of a PARP inhibitor for a biomarker unselected prostate cancer indication, and we are concerned that the efficacy evaluation in TALAPRO-2 may be insufficient to support this new broad indication.

The applicant has presented preclinical data to provide rationale for why the combination of a PARP inhibitor and an ARPI might be effective in patients even without HRR mutations. The FDA considers these preclinical studies primarily to be hypothesis generating, and we acknowledge that they

provide a rationale for the evaluation of talazoparib with enzalutamide in patients without tumor HRRm in clinical trials; however, mechanistic rationale alone is not adequate for drug approval.

It is unclear to us whether the applicant's mechanistic rationale is sufficient to overcome clinical trial design issues with TALAPRO-2, as well as consistent evidence of reduced or no efficacy for PARP inhibitors in non-HRRm mCRPC that has been demonstrated across all relevant trials in the field.

This slide presents an outline of the FDA's main review issues for this application, which we will return to throughout the presentation. First, TALAPRO-2 included a large biomarker-negative population comprising approximately 70 percent of the intended trial population that was incompletely defined and was not formally tested for efficacy.

Second, the interpretation of the overall survival, or OS, results, and their applicability to the current U.S. standard of care are unclear. Third, the addition of talazoparib to enzalutamide

results in added hematologic toxicity versus enzalutamide alone. And fourth, numerous trials of other PARP inhibitors did not support an all-comers indication and, hence, do not provide supportive evidence.

Next, I'm going to discuss the overall design of the TALAPRO-2 trial which provides the primary evidence for the sNDA currently under discussion, as well as for the initial approval of talazoparib with enzalutamide for HRRm mCRPC.

TALAPRO-2 was a randomized, double-blinded, placebo-controlled clinical trial and two cohorts of which Cohort 1, all-comers cohort boxed in red, is the focus of today's discussion. Cohort 1 randomized 805 patients with mCRPC, regardless of biomarker status, in a 1 to 1 ratio to receive talazoparib with enzalutamide or placebo with enzalutamide. Randomization was stratified by HRRm status classified in only two categories as either HRRm or non-HRRm/unknown, together. Importantly, the study did not separately stratify non-HRRm versus unknown subgroups. Additional patients with

HRRm were enrolled later in a separate HRRm cohort that is shown below Cohort 1.

This slide shows the key efficacy endpoints and statistical testing plan for TALAPRO-2. The Venn diagram illustrates the overlapping populations between the Cohort 1, all-comers cohort, which included some patients with tumor HRRm, and the HRRm population, which includes additional patients with tumor HRRm.

The primary endpoint of TALAPRO-2 was radiographic progression-free survival, or rPFS, assessed by blinded independent central review, or BICR, in the all-comers population and in all patients with tumor HRRm. You can see that the overall alpha for the study was split between these hypotheses to control for type 1 error.

A key secondary endpoint was OS in the all-comers population and in all patients with tumor HRRm, which would be tested in a hierarchical fashion if the respective rPFS endpoints were met. Importantly, efficacy for the subgroup of patients with biomarker-negative status was not formally

tested.

Here are the key findings that supported the initial approval of talazoparib with enzalutamide for patients with HRRm mCRPC based on TALAPRO-2, which occurred on June 20, 2023. As shown in the table, biomarker status appeared to predict both rPFS and OS benefit, with the largest benefit seen in patients with tumor BRCAm on the right, followed by the overall HRRm population, followed by non-HRRm/unknown, which appeared to experience the least benefit. The OS endpoint was immature at the time of the initial review.

Ultimately, the review team concluded that the benefit-risk evaluation for the non-HRRm/unknown subgroup was not sufficiently favorable in the context of a broad indication, increased toxicity of the combination versus enzalutamide monotherapy, and immature OS; therefore, the initial approval was limited to patients with HRRm mCRPC.

This slide presents the major difference between the sNDA under discussion and the previous

approval, which is the final OS data. We can see that there was a statistically significant improvement in OS for talazoparib with enzalutamide versus placebo with enzalutamide in the Cohort 1 all-comers population with a hazard ratio of 0.8.

Now, we'll start discussing the main review issues, with the first one being that TALAPRO-2 included a large biomarker-negative population that was incompletely defined and was not formally tested for efficacy.

As background, 20 to 30 percent of patients with mCRPC are estimated to have tumor HRRm, meaning that 70 to 80 percent do not have documented tumor HRRm. TALAPRO-2 met its primary and key secondary endpoints in the all-comers population; however, as we will discuss in greater detail later in the presentation, a preponderance of data, including data available at the time the trial was designed and also from TALAPRO-2 itself, provides strong biological rationale that PARP inhibitors are more efficacious in biomarker-positive tumors.

When there is a high prevalence of biomarker-negative patients who are expected to benefit less than biomarker-positive patients, it is both important and feasible to design the study to reliably characterize the benefit-risk ratio for these biomarker-negative patients.

Another important issue related to biomarker subgroups in TALAPRO-2 is how they were defined. There was incomplete prospective determination of biomarker status such that the non-HRRm/unknown stratum was not a true biomarker-negative population. I'll start with the pie chart on the left, which illustrates the prospective testing results that were available prior to randomization and were used for stratification. These consisted mostly of tissue testing.

ctDNA testing was made available after the start of the study through a protocol amendment, and only 55 patients out of the 805 total patients had ctDNA results prior to randomization. The testing results at the time of randomization and stratification included 26 percent of patients with

unknown biomarker status who were combined in the same stratum with patients with one or more negative tests despite the lack of any clear biological justification to do so. 685 patients had ctDNA results that were obtained prior to treatment but became available only after randomization, as denoted in this middle category of prescreening/screening results.

Finally, the pie chart on the right represents even more ctDNA testing results that were obtained after screening, including from patients who received more than one ctDNA test over the course of the study. You can see that the proportion of patients with unknown biomarker status decreases as the amount of testing increases, and approximately 160 patients who were initially classified as having non-HRRm or unknown status were later reclassified as having tumor HRRm.

The incomplete prospective determination of biomarker status and large percentage of patients with unknown status at randomization adds to

uncertainty about whether patients with true non-HRRm status are really benefiting from talazoparib. Furthermore, there was no single definition of biomarker negativity that was incorporated into the formal statistical analysis plan, and various definitions can be used in post hoc analyses.

Here, we consider two potential non-HRRm subgroup definitions, a single-negative subgroup defined as having only one negative test result from either tumor tissue or ctDNA testing, and a double-negative subgroup defined as having negative results from both tissue and ctDNA testing. Again, to be clear, the single- and double-negative designations refer to the number of testing modalities for which patients had a negative testing result, with negative results from two different testing modalities presumably indicating a higher likelihood of being truly negative for tumor HRRm.

The overall study population depicted in these pie charts also includes the HRRm subgroup

where patients had to have at least one positive test and the unknown subgroup consisting of all remaining patients. The applicant's definition of non-HRRm used in their post hoc analysis is the double-negative subgroup in the middle pie chart based on prescreening/screening results.

The FDA looked at another definition of double negative, shown in the right pie chart, which was based on all available testing results. We can see that the numbers of all four subgroups change as more testing becomes available, and the presence of multiple potential definitions and time points of sample availability introduces confusion when looking at post hoc analyses.

On this slide, we can see the rPFS results for the non-HRRm/unknown stratum on the left, along with post hoc analyses of rPFS using the applicant's definition of double negative in the middle, and the FDA's definition on the right. We can see that all three of these analyses produce consistent results for the rPFS hazard ratio.

Given that the double-negative subgroup was

not stratified, there's a higher risk that the baseline characteristics may have differed between treatment arms; therefore, FDA conducted additional sensitivity analyses to adjust for known differences in baseline characteristics, which were not shown here but were supportive of these analyses. Even though FDA was able to reproduce the applicant's exploratory analyses of rPFS, a major caveat to drawing conclusions from these analyses is that there was no formal statistical testing in the large biomarker-negative subgroup.

Next, I will discuss why the lack of formal testing in patients with non-HRRm tumors is problematic.

Exploratory subgroup analyses are generally conducted to ensure consistency of the treatment effect across subgroups of interest; however, assessing a large number of exploratory subgroups will inevitably lead to random high and random low observations; therefore, interpretation of subgroup analyses is limited without a prespecified formal statistical testing plan to control for the chance

of making a false positive conclusion, otherwise known as type 1 error.

To put this another way, without formal statistical testing, it is challenging to conclude whether the exploratory results of the large non-HRRm subgroup in TALAPRO-2 represent a true treatment effect or whether any apparent effect could have occurred due to randomness or chance.

All exploratory subgroup analyses should be interpreted with caution. Exploratory results that appear favorable, even with a large apparent magnitude of effect, may not be confirmed by a subsequent dedicated trial. Caution is especially warranted when the biomarker-negative population is a large proportion of the overall population and the biomarker is known to be a strong predictor of treatment effect.

Formal testing in the large non-HRRm subgroup in TALAPRO-2 should have been feasible, but as is, treatment of the non-HRRm subgroup with talazoparib might expose these patients to additional toxicity despite the lack of a

statistically convincing result.

When there's an expected differential effect based on biomarker status, trial design options include assessing the biomarker-positive and biomarker-negative subpopulation separately. This could include a two-trial approach, as shown on the left, or a separate cohort approach, as shown on the right. Regardless of the trial design that is used, it is important to ensure adequate prospective determination of biomarker status prior to randomization. This helps avoid heterogeneous unknown populations where efficacy is difficult to interpret.

Additionally, formal testing for each biomarker population should be performed with adequate power and sample size. For designs where biomarker-positive and biomarker-negative subpopulations are studied separately, full alpha, for example, two-sided alpha of 0.05, can be allocated to each separate biomarker-defined subgroup. This lessens the possibility of false positive results while still maintaining adequate

power to detect a true effect.

TALAPRO-2 did not fully address these key trial design principles since biomarker status was incompletely specified prior to randomization and biomarker-negative patients were not formally tested.

Now, we'll move on to the next review issue, which is the interpretation of the TALAPRO-2 OS results and their applicability to the current U.S. standard of care are unclear. As a reminder, the positive final OS results in the all-comers population were the major reason for the submission of this sNDA.

First, as Dr. Fallah mentioned previously, there's a clear differential effect in OS by biomarker status, with the positive results in the all-comers population appearing to be mainly attributable to the HRRm stratum on the left, while the curves are much best separated in the non-HRRm/unknown stratum on the right.

We already mentioned caveats that the OS was not formally tested in the non-HRRm/unknown

stratum, and also that this stratum included patients with unknown biomarker status. But even looking at the non-HRRm/unknown data shown here at face value, the hazard ratio of 0.88 is challenging to interpret given that the Kaplan-Meier curves crossed multiple times and do not follow proportional hazards assumption. The median OS improvement of 7 months may also be an overestimate due to heavy censoring.

Second, as illustrated in this table, interpretation of the all-comers OS result is challenged by the fact that only a small proportion of patients in the Cohort 1 control arm received a subsequent PARP inhibitor. This includes patients who had demonstrated HRRm or BRCAm, who currently have available options for subsequent PARP inhibitor monotherapy with known clinical benefit.

Olaparib was approved in 2020 as monotherapy for HRRm mCRPC after progression on an ARPI like enzalutamide, and this should have been available for many patients on TALAPRO-2 after progression. In the PROfound trial, olaparib treatment resulted

in both an rPFS benefit in the overall HRRm population and a statistically significant OS benefit attributable to the BRCAm population. If patients in the TALAPRO-2 placebo arm with tumor HRRm, and particularly those with BRCAm, had received subsequent olaparib, the statistically significant all-comers OS improvement observed in TALAPRO-2 might have been lessened.

I want to be clear that treatment with subsequent PARP inhibitor applies exclusively to patients with HRRm, and as we said, the biomarker-positive patients appeared to largely drive the positive OS results in the all-comers cohort. The relevance of the all-comers OS result to patients with non-HRRm is not clear, other than that these subpopulations were lumped together in the same all-comers cohort.

A dedicated cohort or trial in patients with non-HRRm tumors would have provided a more certain estimate of any potential OS benefit in this subpopulation, both because it would have enrolled a more homogeneous group of patients and also

because patients with non-HRRm tumors are not indicated to receive subsequent PARP inhibitors.

Third, I'll briefly make a point about the OS results in patients with non-HRRm tumors that ties back to topics I mentioned earlier, including variable definitions of HRRm negativity and the need for caution when interpreting exploratory post hoc subgroup analyses.

These figures show exploratory OS analyses in two subgroups of patients with non-HRRm tumors based on the FDA's definition using all available testing results. The first figure shows a potential OS benefit of large magnitude in patients with double-negative testing results; however, the figure on the right, which shows results in patients with single-negative or unknown testing results, appears to show lack of OS improvement. This is counterintuitive given the way the groups were defined, since the single-negative or unknown subgroup might logically have more patients with undetermined HRRm and should, therefore, have a more favorable hazard ratio than the

double-negative subgroup. Instead, the opposite is true.

This comparison illustrates that one or both of these exploratory subgroup results may be due to imbalances of confounding baseline factors and not due to true treatment effects or lack thereof. It is possible to conduct exploratory sensitivity analyses to correct for known differences in baseline factors, but there may be unknown and unmeasured differences that still affect the efficacy results in unpredictable ways. Overall, the counterintuitive subgroup results shown here contribute to the uncertainty of OS interpretation in the non-HRRm subpopulation.

Now, I'll move on to the third review issue, which is that the addition of talazoparib increases hematologic toxicity versus enzalutamide alone.

These figures illustrate that the addition of talazoparib to enzalutamide, as shown in the blue bars, substantially increases toxicity over placebo with enzalutamide, as shown in the orange bars. On the left, we can see that the incidence

of high grade and serious adverse reactions is substantially increased with talazoparib. Fatal adverse reactions were similar between treatments, or even slightly more common in patients receiving placebo. On the right, we can see that treatment discontinuations, treatment interruptions, and dose reductions due to adverse reactions were all much more common with talazoparib than with placebo. Much of the increased toxicity in patients receiving talazoparib in TALAPRO-2 can be attributed to hematologic toxicity.

Here, we can see high and substantially increased incidence of both all grades on the left and grades 3 to 4 hematologic toxicity on the right in patients who received talazoparib. Forty-two percent of patients receiving talazoparib required a red blood cell transfusion, including 25 percent who required more than one transfusion. Another important safety consideration related to hematologic toxicity is that myelodysplastic syndrome and acute myeloid leukemia are class effects of PARP inhibitors. One case of each was

reported for patients treated with talazoparib in TALAPRO-2 versus no cases for patients treated with placebo.

An important question is whether any degree of additional toxicity or patient burden from a second medication is justified in the patient population without tumor HRRm given that the added efficacy of talazoparib in these patients may still be uncertain. Because talazoparib is an add-on to effective therapy in enzalutamide, it is not possible to establish the effectiveness of talazoparib on an individual patient level. Even if talazoparib was adding no efficacy for a given patient, that patient might still have a durable response due to enzalutamide alone. For this patient, talazoparib might be adding toxicity without efficacy, which we've termed here a toxic placebo.

Since we cannot determine the added effect from talazoparib for any individual patient, we are entirely dependent on clinical trial results to determine whether it is a treatment effect that

would justify the added toxicity from talazoparib in patients with non-HRRm mCRPC.

Now, I'll move on to the fourth review issue, which is that other trials of PARP inhibitors did not support an all-comers indication.

This slide shows key trials of other PARP inhibitors in prostate cancer that included both biomarker-negative and biomarker-positive patients and showed reduced or no efficacy in patients without tumor HRRm. The first row corresponds to TOPARP-A, which was an exploratory, single-arm, phase 2 trial of olaparib monotherapy in patients with or without HRR mutations.

The primary endpoint was a composite response endpoint that I've defined below the table. Responses were seen in 88 percent of patients with tumor HRRm and in only 6 percent of patients without tumor HRRm. The second row corresponds to PROpel, which was a randomized phase 3 trial of olaparib with abiraterone acetate and prednisone versus placebo with abiraterone

acetate and prednisone.

As was extensively discussed at a prior advisory committee meeting, benefit in the primary endpoint of rPFS appeared to be primarily attributed to the subgroup of patients with BRCAm tumors, resulting in the restriction of the indication to this smaller patient population.

Finally, the third row corresponds to MAGNITUDE, which I will discuss more extensively in the next slide. But suffice to say for now that patients with non-HRRm tumors were formally studied in this trial and did not show added benefit from adding olaparib to abiraterone acetate and prednisone. This resulted in restriction of the indication to BRCAm mCRPC.

To focus more on MAGNITUDE, this was a randomized phase 3 trial of olaparib with abiraterone acetate and prednisone versus placebo with abiraterone plus prednisone. The design of this trial was more consistent with the preferred design for biomarker-selected populations, as I described before. Specifically, the non-HRRm

population was studied in an entirely separate cohort with formal statistical testing and appropriate alpha control. As shown in the red box, the non-HRRm cohort was stopped early due to futility, with a hazard ratio of slightly over 1 for composite progression events.

There are clear caveats to comparing the results of MAGNITUDE directly to those of TALAPRO-2, including that these were different trials and that both the PARP inhibitor and the ARPI were different between trials. Still, it is worth noting that the trial in the same disease area that is closest to a preferred design did not show added benefit of a PARP inhibitor in biomarker-negative patients. MAGNITUDE also demonstrates that it's feasible to conduct such a trial in this disease space.

Several additional trials of PARP inhibitors in prostate cancer have excluded patients without tumor HRRm entirely. This includes the applicant's own trial, TALAPRO-3, which studies talazoparib with enzalutamide in patients with HRRm metastatic

hormone-sensitive prostate cancer or mHSPC. The restricted eligibility criteria for many trials suggest a broad understanding in the field, including by the applicant, that there is differential sensitivity to PARP inhibitors based on biomarker status, with reduced or no sensitivity in patients with non-HRRm tumors.

We would argue that a preponderance of data, even including data from TALAPRO-2 itself, consistently support differential sensitivity to PARP inhibition based on biomarker status. We show here the results of the primary rPFS analysis and the updated OS analysis of TALAPRO-2 Cohort 1, which show a clear trend in efficacy by biomarker status.

Similar to what I showed before with the interim OS results, patients with tumor BRCAm, shown in the right column, appear to benefit most in terms of both rPFS and OS, followed by the overall subgroup of patients with tumor HRRm, followed by patients with non-HRRm or unknown status who appear to benefit least. Although the

results of the larger Cohort 2 HRRm population are not shown here, they were very similar to the results of the respective subgroups of Cohort 1.

The fact that the efficacy of talazoparib with enzalutamide appears to differ based on biomarker status, in a similar way to other trials of PARP inhibitors in prostate cancer, supports that the biomarker-negative subgroup should have been formally tested in TALAPRO-2.

With that, I will present a final summary slide that highlights uncertainty in the evaluation of talazoparib with enzalutamide in non-HRRm mCRPC.

First, we'll start with the trial itself.

TALAPRO-2 evaluated the heterogeneous all-comers population with a suboptimal design for biomarker-negative patients. Second, the interpretation of the OS results and their applicability to the current U.S. standard of care are unclear. Third, the addition of talazoparib increases hematologic toxicity versus enzalutamide alone, and unnecessary toxicity in a broad patient population is a major risk of uncertain study

results.

Finally, the supporting data are conflicting and of unclear strength. In particular, it is unclear whether the mechanistic rationale presented by the applicant is sufficient to overcome the clinical trial design issues and differences in efficacy by biomarker status across all relevant trials of PARP inhibitors in mCRPC.

The topic for discussion is whether efficacy should be formally evaluated in a biomarker-negative population when the biomarker is predictive of response and the prevalence of the biomarker-negative group is high.

And finally, the voting question is, are the TALAPRO-2 results sufficient to conclude a favorable benefit-risk profile for adding talazoparib to enzalutamide in patients with non-HRRm mCRPC?

Thank you for your attention, and this concludes my presentation.

Clarifying Questions

DR. SPRATT: Thank you. FDA also gets

brownie points for finishing early.

We will now take clarifying questions to the presenters. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Are there any clarifying questions for the presenters?

I will start, and remember to put your name tag up if you have a question. I'm Dan Spratt from UH Seidman, Case Western. This is for the FDA. If you could pull up slide number 7, and look at the overall survival in non-HRRm/unknown, the bottom right.

So, it was mentioned in the last presentation that proportional hazards have been

violated, but throughout this presentation, you guys didn't provide us with restricted means survival times. We heard from the applicant there are survival time benefits of 7 months, 9 months, 12 months. Does the FDA have an RMST for this curve here?

DR. SUZMAN: Daniel Suzman, FDA. Our statistical team did do our RMST analyses, which showed a slightly improved OS for the talazoparib-containing arm. If you'd like more details, I can ask them to come up to the microphone.

DR. SPRATT: Yes.

DR. FIERO: Mallorie Fiero, FDA statistics. Our statistical team did perform RMST analyses for overall survival, given there's challenging interpretation for overall survival in this subgroup. For the non-HRRm subgroup, the mean difference, based off of RMST, ranged from 0.2 to about 1.6 month difference. This is a bit of a smaller difference compared to the Kaplan-Meier estimates. And in comparison, the HRRm estimates

for the subgroup ranged from about 4.8 to 8.8.

I want to also caveat that the difference also is highly subjective to the timing of the analysis or duration of follow-up. So for this reason, these analyses are considered exploratory. Thank you.

DR. SPRATT: Thank you. Dan Spratt, UH Seidman. So, let's just say 36 months, and basically, for patients that have been treated in both arms up to 36 months -- I mean, the curves are on top of each other -- there's less than a 1-month prolongation in their mean survival time.

DR. FIERO: Yes.

DR. SPRATT: It's not 9 to 12 months.

DR. FIERO: Yes. Mallorie Fiero, FDA statistics. To clarify, it was about 0.2 months at 36 months and about 1.6-month mean difference at 66 months, which is the time in which both treatment arms were followed. Thank you.

DR. SPRATT: Thank you.

I'll allow, if anyone from the applicant side wants to respond to the RMST question,

otherwise, we'll go on to the next clarifying question.

DR. KENNEDY: Dana Kennedy, GU Development Head, Pfizer Oncology. I'd like to ask Dr. Yang to the podium to respond to that question.

DR. YANG: Yuquing Yang, Pfizer statistics. I would like to first address your question about proportional hazard. As a sponsor, we examined the proportional hazard assumption for this non-HRRm/unknown subgroup, and we used the Suprema test to evaluate that. The p-value for the Suprema test for this subpopulation is 0.343, which indicates there's some violation to the assumption; however, not significantly. And to our knowledge, with mild to moderate violation, the Cox regression is not invalidated and, therefore, the estimate for hazard ratio from the Cox model is still valid.

I want to add, on top of the RMST, as a sponsor, we also evaluated the MaxCombo test, which is another commonly used method under non-proportional hazard. With the MaxCombo test, the p-value is very similar to what we observed

from the log-rank test. Thank you.

DR. SPRATT: Thank you.

DR. PAZDUR: I'd just mention one thing. Before we start talking about magnitude of difference in this non-HRR population, I think it's important to say we did not have a statistical plan here to test this. So before we start talking about magnitude, we've got to answer an essential question. Is there a difference? And unless you can establish is there a difference, then all of this discussion of magnitude of effect on overall survival or PFS is really subject to a lot of debate.

And I'd like to point out, some of the p-values that were put on these slides were not formally tested and cannot be interpreted. And I did note Pfizer put in micro type there that it was compared to a nominal p-value of 0.05. There is no formal testing of those p-values, so they should be interpreted as purely exploratory.

DR. SPRATT: That was Dr. Pazdur from the FDA.

DR. PAZDUR: Yes.

DR. SPRATT: Yes?

DR. FIERO: Yes. I wanted to add -- Mallorie Fiero, FDA statistics -- the MaxCombo test is not formally prespecified, so we do consider it exploratory.

The second point I wanted to make is in addition to any test for non-proportional hazards, the Kaplan-Meier curves are indicative of potential violations. So we don't only look at an exploratory test for non-proportional hazards, the Kaplan-Meier curves are very evident.

The last point I wanted to make is that a large proportion of these patients in this subgroup have unknown status, so it is very difficult to interpret that unless we have complete ascertainment of biomarker status. Thank you.

DR. SPRATT: Thank you.

We'll go to Dr. Madan.

DR. MADAN: Thank you, Dr. Spratt.

DR. SPRATT: State your name and affiliation, please.

DR. MADAN: Sorry. Ravi Madan, National Cancer Institute. I have a question for the sponsor. It's about subsequent therapies. If we could pull up slide CU-4 from the sponsor, I'd like to have a couple comments on this.

This is my interpretation of this slide. While the date on the publication here is 2024, the data was collected from Medicare database between 2014 and 2019. This is really a study of subsequent chemotherapy after first-line therapy in prostate cancer, so I don't think it applies to prostate cancer practice in 2025 because now second-line therapy is no longer chemotherapy, nor do I think the BRCAAway is the correct Dr. Maha Hussain trial, the reference for the potential subsequent PARP inhibition therapy beyond first or second line.

I would actually reference the PROfound trial, which had an 81 percent crossover rate in that trial, and that was third or fourth line. So I think sometimes we overplay this older data from when people were reluctant to give chemotherapy.

But getting to the point of the unselected group, and perhaps I missed this, what were the subsequent therapies of the unselected groups of patients in this study?

DR. KENNEDY: Dana Kennedy, Pfizer Oncology GU Development Head. I'd like to first ask Dr. Barata to the podium to speak to your specific critique of the data that's presented here.

DR. BARATA: Yes. Thank you so much. Pedro Barata, Cleveland, Ohio, Case Western.

So the comment was made regarding whether or not these data reflect the reality. I would just point out these data from Steve Freedland. We could have brought up many other data sets, including the paper that just came out last month from the VA, far more contemporary.

We can pull up, for example, slide DB-2, please. The point is, we have seen, perhaps unfortunately, significant consistency in access to subsequent therapies for patients being treated for first-line mCRPC. That data has not changed significantly over time. And as time goes by, we

have data from different real-world data sets -- Medicare VA, SEER -- and Dr. Agarwal was part of the development of that data as well. But bottom line, altogether, we do see that about half of the patients are able to proceed with subsequent therapy.

DR. MADAN: So, I would actually just highlight that this is the same data. This looks like a figure from the same paper. So I don't think it's different than what the other one showed.

DR. SPRATT: Real quick, Dr. Madan. I just want to make sure they can address the question you had on what were the subsequent lines of therapy.

Thank you, Dr. Barata.

DR. BARATA: Thank you very much. Pedro Barata, Case Western. Can we please pull up the slide in regards to the breakdown of subsequent therapies?

And the question is regarding the real-world data set. I'm assuming that they're not specifically for the upper two.

DR. MADAN: Okay.

DR. BARATA: While we wait for those slides, in regards to the real-world data set that Dr. Madan alluded to, the access to subsequent therapies for patients treated with first-line ARPIs, which is a vast majority of those patients, was over 60 percent.

Patients undergo to receive also another ARPI. As I believe it was alluded to, in the single, we have use of chemotherapy that's between 10 to 25 or so percent. I'm quoting those numbers. Overall, we have access to other therapies in the single digits. That includes PARP inhibition, that includes radioligand pharmacy compounds, particularly lutetium PSMA, and other lines of taxane, first-line docetaxel, but also cabazitaxel, as well as radium.

All those life-prolonging therapies available, we used beyond first-line mCRPC in all the different real-world data sets. And we can get the data about the other real-world data sets as requested. It does show that breakdown, more ARPIS

than all the other therapies available. Thank you so much.

DR. SPRATT: Dr. Madan?

DR. MADAN: Yes. It was good data, I think somewhere between 45 and 50 percent. I would just say that, obviously, real-world data is not what we want it to be, but I also would say that a contemporary trial, PSMAfore [ph] for example, had a crossover rate to third-line therapy after either ARPI or lutetium of about somewhere I think around 75 or 80 percent.

So I think this is challenging for me to understand how to apply this in 2025 when our patients have access to more therapies. Lutetium, for example, was now approved pre-chemotherapy recently.

DR. SPRATT: Dr. Madan, I'm just going to interrupt you. We will have time for discussion.

DR. MADAN: Yes.

DR. SPRATT: This is just for the clarifying questions.

DR. MADAN: Yes, you got it. That's all for

my question.

DR. SPRATT: Okay. Thank you. I'm going to keep moving on.

Dr. Tendler?

DR. TENDLER: Hi. Craig Tendler, industry representative, and a clarifying question for the FDA.

I take the point that everything outside of the prospectively defined stratified subgroups are exploratory and certainly can be due to chance alone. I'm just challenged a little bit with how to define a pure biomarker-negative population in the real world because we hear that less than 50 percent are tested. There are quality issues. Sometimes it's positive by ctDNA, not by tissue, and vice versa.

What I'm left with is all those other subgroups, and you can't really interpret them because they're fraught with all sorts of other challenges. Then, is there such a thing as a pure biomarker-negative study? So I'm left with this real-world type of study, where this is what

happens in the real world.

So I'm just trying to get your sense as to is this something that is an absolute, has to be, for considering this type of approval, or are you left with something where we look at the prospectively defined stratified subgroup where we still see a statistically significant advantage in rPFS and an attenuated OS treatment effect of 0.88, and then we're left to interpret that versus the risk?

DR. SUZMAN: Sure. Daniel Suzman, FDA. I guess the first point I would make is that we're not running a trial in the real-world population. We're running a clinical trial that needs to determine the efficacy in this population. So from that perspective, it's important to adequately prospectively define and determine your biomarker status. In this case, there were a large proportion of patients with unknown biomarker status.

Again, there are various ways that I think the community would be willing to define biomarker

negative, but there needs to be a clear definition upfront with full prospective determination and, again, alpha control and formal testing to really determine the efficacy of a therapy in that specific biomarker-negative population.

DR. SPRATT: Thank you.

Dr. Pazdur?

DR. PAZDUR: I just want to address that. That's clinical medicine, basically. And sometimes when you're seeing an individual patient, you have to re-biopsy a patient if you really want that information, do another blood test, whatever. But that's the real world, so to speak, and that's clinical practice.

This is not what we're talking about here. We're asking to extend an application, really, a new indication to a huge indication, 70 percent of men with castrate-resistant process state cancer. This is a big population. We need robust information. And what we have now to extend that to a new indication of a non-HRR population, however you want to define that -- but here again,

this is the way it was defined in this population -- is a population that was really not tested at all statistically.

So in essence, to put the elephant in the room, this would be like somebody coming to us for a huge indication, 70 percent of this population, coming to us with a randomized study, having it completed, and then saying, "Oops. I forgot to do a statistical analysis plan."

This is really what was done here. We do not have confidence of what these results are. And here again, if we were dealing with a small number of patients here, a rarer population -- we've demonstrated, I think in oncology, this regulatory flexibility, and have been criticized for it and applauded for it. But in this situation, where you're talking about a huge number of patients, you don't need proof. You need robust proof of this.

Here again, I don't know if this is a chance finding at all. I do want to emphasize, do not talk about the magnitude of benefit unless you are able to demonstrate is there an effect here. But

this is not that dissimilar as somebody coming in and doing an analysis of a study after it is done. So it is tantamount to somebody shooting an arrow on the wall, and then painting a target around it. I do not know what this represents, and I really do have a big problem with these p-values that were presented by the sponsor. I just think that that is, to be honest with you, not consistent with a large pharmaceutical company's presentation to an advisory committee.

DR. SPRATT: Thank you, Dr. Pazdur.

Just to say again, we will have time for discussion questions. This is for clarifying questions.

DR. TENDLER: Yes. I just had one other clarifying question for the applicant.

In slide CE-12, we see the secondary endpoints, and, again, this is specifically in that cohort of double-negative, non-detectable HRR and, again, maybe can be accused of cherry picking.

Have you done the same analysis for the actual stratified subgroup and the prospectively

defined non-HRR mutant subgroup, and is that consistent? Because again, some of those endpoints -- and it's not overall survival, but I think things like first time to cytotoxic chemotherapy are clinically relevant in this population. Most patients don't want to receive taxane chemotherapy. Things like confirmed CR would be key secondary endpoints.

So this that was shown to us was in the exploratory one. Is it consistent with the stratified subgroup?

DR. KENNEDY: Dana Kennedy, GU Development Head, Pfizer Oncology. Yes, we have done those analyses in the other secondary efficacy endpoints for the prespecified subgroup of HR negative or unknown, and they are very consistent with what we see in the exploratory subgroup of no detectable HR gene alteration by both ctDNA and tissue.

I'd like to take a moment also to address the various definitions of non-HRR gene alterations that have been presented today because I think it does potentially introduce some confusion, and I

think we want to clarify any confusion around the various definitions that have been used. Slide up, please.

DR. SPRATT: Sorry to interrupt you.

Does anyone have a clarifying questions on the definitions of HRRm? You guys both, I think, did an amazing job presenting this. I just want to make sure, does anyone have a question on the definitions?

(No audible response.)

DR. SPRATT: I think we're ok. I don't think we need to go back through the different definitions of --

DR. KENNEDY: Sorry. Just to clarify, there are various definitions, but I wanted to put the results into context for the panel to be able to observe that the differences between these various definitions are very modest.

So if we go from the top of the forest plot to the bottom, at the top is FDA's definition using all available tests, both prospective as well as retrospective tests that were obtained at baseline,

as well as on treatments. We see a hazard ratio of 0.68 for rPFS.

Using the applicant's definition of all baseline samples, we also see a very consistent result. When we look prospectively by tumor tissue and blood, again, consistent results. When we look at the prospective plus retrospective ctDNA that was collected at baseline, as well as by just tumor tissue, and then just ctDNA, in practice, patients will likely only have one test available to them if they have a test at all, so understanding the results by tumor tissue alone, by ctDNA alone, are important.

DR. SPRATT: Thank you so much.

I'd like to just move on.

Dr. Graff?

DR. GRAFF: Hi. Julie Graff, Portland VA and OHSU. I'll note that both preclinical and clinical data comparing the PARP inhibitors was given, and the preclinical data supported talazoparib as a better PARP-trapping agent.

I'm asking both sides, mostly this side,

Pfizer, how reasonable is it to do a cross-study comparison looking at TALAPRO-2 and PROpel?

DR. KENNEDY: Dr. Agarwal?

DR. AGARWAL: Neeraj Agarwal, Huntsman Cancer Institute. I just want to make sure I got the question correctly, Dr. Graff. Why did we perform cross-trial comparisons?

DR. GRAFF: Do you feel it's reasonable to compare those two studies?

DR. AGARWAL: Well, we saw the comments from the FDA, and the PROpel trial was brought up, and it was brought up that TALAPRO-2 data are not consistent with the previous trial results. And that was the reason for showing the cross-trial comparisons, showing that activity across the subgroups were more pronounced with the combination of talazoparib plus enzalutamide. So that was the only reason we performed the cross-trial comparisons.

DR. MORGANS: Alicia Morgans, Dana-Farber.

Thank you for the question, Dr. Graff. I actually don't think it's especially reasonable to

make this kind of a cross-trial comparison, and the reasons are that the preclinical data did suggest that there actually is difference between these PARPs. But there's also difference between the androgen receptor signaling inhibitors, or pathway inhibitors, such that one is an AR antagonist and one is, as we heard, really an androgen receptor synthesis inhibitor which decreases the ligand but does not directly antagonize the receptor.

So I think that this kind of a cross-trial comparison is interesting in generalities; that we did see similar rPFS prolongation even in the unselected population within PROpel, actually, but when we look at the drugs themselves, there's probably a difference; otherwise, they would be the the same agents. Thank you.

DR. SPRATT: Thank you.

Dr. Conaway?

DR. CONAWAY: Yes. Could we have slide CE-14, please? Mark Conaway, University of Virginia. This is a question for Dr. Kennedy, and I believe Dr. Maguire addressed this as well.

I'm really confused by the gray boxes here. As you pointed out, people are either HRRm mutated or not, so it would seem like the results in the bottom one would be a mix of the bars above it; that there would be some positive, some negative, and that the average should be somewhere in between. And that makes sense for the blue bars; they're more or less the same, but there's a huge difference in median survival in those with HRRm undetermined, whereas it's the test that's not undetermined. They're actually have positive or negative mutation.

So how do you explain this large effect on survival by the fact that the test is undetermined?

DR. KENNEDY: Dana Kennedy, Pfizer Oncology GU Development Head. So we do agree that the control alarm in this HRRm undetermined subgroup did overperform relative to what we would expect with enzalutamide alone in this population.

Could I have slide CE-13 up please?

We did also observe in the undetermined group some imbalances in baseline prognostic

factors that would suggest that the control arm had a better prognosis compared to the combination arm in this subgroup. We see this reflected in rPFS, most prominently where performance of the control arm was a median of 27.6 months, almost 8 months longer than what we would expect with enzalutamide with historic controls. But we still see benefit compared to the combination.

If we could go back to CE-14, we, however, don't see this difference translated for overall survival in this subgroup. Again, we want to focus on the groups where we have the most confidence in their genomic profile, those with an HR gene alteration or those without an HR gene alteration by the most stringent definition, which is negative by both ctDNA and tissue. And in those subgroups, we see benefit.

DR. CONAWAY: It just seems to me that it gives an idea, going back to Dr. Pazdur's point, of how big a difference you can see after the fact, based on something, whether the test was determined or not, but thank you. That's my question.

DR. SPRATT: Thank you.

We have time. I have a couple more questions. If you can pull slide 36 from the FDA; and this is Dan Spratt from UH Seidman, Case Western. Great.

So when you look here on the left, in the HRRm, effectively, the survival curves immediately separate -- I'm just eyeballing it; let's call it 20 percent -- and they pretty much just maintain throughout the entirety of the curve. But in the non-HRRm, they pretty much stay completely together until 36 months and, again, sample size starts reducing. But then we'll just pretend there's a separation even though, as we've said repeatedly, it wasn't powered, the magnitude, all the things that you've already heard.

But I'm just curious. How do you explain this, that the survival curves separate immediately in HRRm, but it's after 3 years in this non-HRRm population?

DR. KENNEDY: I'd like to ask Dr. Agarwal to the podium to respond to that.

DR. AGARWAL: Neeraj Agarwal, University of Utah. Obviously, this is a mixed subgroup. HRR mutation undetermined patients are definitely playing a role here as far as overlap of the curve is concerned. So if you look at the exploratory analysis, looking at non-HRR mutation patients, there's a clear separation of the curve, but then HRR undetermined status patients, enzalutamide was performing better. So it is definitely a mix of those two populations, which is causing this relative overlap of the curve early on.

I have another thought behind this. Number one, if you look at the forest plot for overall survival, we consistently see higher magnitude of benefit in patients who have more aggressive disease, so high Gleason score, patients who had de novo disease at the time of initial presentation -- thank you; if you can please bring up the overall survival forest plots -- and patients who received abiraterone in the past, a smaller number of patients.

In my clinic, when I see patients who had

prostatectomy done many years ago, they usually are more likely to have undetermined status on the tissue testing because of the inadequate quantity or quality of tissue. These patients, in my view, are the patients who have a longer time from prostatectomy or radiation therapy to onset of metastatic disease, and then onset of CRPC.

So is it possible that these patients had indolent disease to begin with, which is allowing both arms to perform well, and they may not need talazoparib for these patients?

DR. SPRATT: Thank you.

Yes? FDA?

DR. FALLAH: Another potential explanation --

DR. SPRATT: Please state your name.

DR. FALLAH: Sorry. Jaleh Fallah, FDA. So another potential -- can we go back to that slide, 36, FDA?

The OS curves start to separate around 33 or 36 months. This is around the median rPFS for the talazoparib arm. So it makes me think that after

they had the disease progression on talazoparib, there is something about the subsequent therapy that they received which led to the differences in the overall survival.

DR. SPRATT: Thank you.

I'm going to ask another question, then, because we've got time.

There was a lot of discussion and presentation on the preclinical mechanistic aspects, which obviously that's not sufficient, as we've heard. But what's very surprising that was included in the applicant's packet is, DNA repair status, you don't measure by gene expression, which most of the papers cited. They simply show reduced gene expression.

Functional DNA repair complexes are at the protein level, and they need to be phosphorylated, or ubiquitinated, or something, to have a functional DNA repair complex. And the only study, actually, that you cited that did a functional homologous recombination assay was from Dr. Sawyer's group, the Polkinghorne paper. And in

the paper you guys referenced, they did an analysis, and it showed ARN-509 explicitly does not induce an HR-deficient state. It's a non-homologous end joining state, not an HR-deficient state.

So I'm just curious. Number one, where is the data saying that a potent anti-androgen causes a functional homologous recombination deficient state, not simply reduced gene expression?

DR. KENNEDY: Dana Kennedy, Pfizer Oncology, GU Development Head. I'd like to ask Dr. Laird to the podium to respond to your specific question.

DR. LAIRD: Douglas Laird, Pfizer, translational oncology. I think you've correctly pointed out that some of the papers from the historical literature did focus on expression of the genes rather than functional readout. So we'll request the slide that actually focuses on gamma H2AX readout with talazoparib, if we can have that, since there's more contemporary work with talazoparib, but I think with a direct DNA readout. So bring up slide 1, please.

This is a slide focused on PARP trapping on the X-axis, and on the Y-axis, gamma histone, H2AX, a DNA damage marker, so a functional readout here. And what we can see is it's a log scale for the trapping, and as mentioned before, a 100-fold or 2000-fold difference, or superiority in potency for talazoparib here. And what we can see is this does translate to the gamma H2AX damage marker in a certain consistent function.

DR. SPRATT: Sorry to interrupt you. I believe talazoparib looks amazing compared to the other PARP inhibitors, but the question really is, in a non-HRRm status, they have intact homologous recombination. Do you have any data showing that an anti-androgen induces a functional HR-deficient state? Not that talazoparib is doing what it's supposed to do.

DR. LAIRD: Excellent. Mark Albertella and the AC team showed at the AACR, a couple of weeks back, very nice functional markers or DNA damage, including gamma H2AX and some other markers in looking at the combination of enzalutamide and

saruparib, a selective PARP1 inhibitor. So there, I think they did a very nice job of bridging from the in vitro to the in vivo data, and did in fact show induction, and then they expected an enhanced benefit. Thank you.

DR. SPRATT: Thank you. Appreciate it.

Dr. Madan? Do you have a question, Dr. Madan?

DR. MADAN: Thank you, Dr. Spratt.

Ravi Madan, National Cancer Institute, and just a quick question on slide CS-4 for the sponsor about the toxicities.

We focused a lot on the heme toxicities, but it's hard to ignore that there's a 62 percent increase in nausea and a 31 percent increase in decreased appetite as well. When you have all grades listed here, is it safe to assume that in this trial, grade 1's were not captured, and then the remainder grades would be grade 2? Or did the study have grades 1 and 2 captured; and if it did, do you have the breakdown for decreased appetite and nausea?

DR. KENNEDY: Dana Kennedy, Pfizer Oncology, GU Development Head. We, in fact, did capture all grades of adverse events, as is consistent with practice in clinical trials. What's shown here as all grades is representing grades 1 through 4, but grade 3 and 4 are specifically highlighted in bright blue and red. For nausea, as well as the other adverse events that you mentioned, those are grade 1-2 events.

DR. MADAN: And do you have the breakdown between grades 1 and 2 for those two toxicities?

DR. KENNEDY: I don't have that at the moment, but I can get that to you after the break.

DR. MADAN: Okay. Thank you. That's the end of my question.

DR. PAZDUR: I have a question for the FDA.

(Laughter.)

DR. SPRATT: This is Dr. Pazdur again.

DR. PAZDUR: Yes. This is my own personal bugaboo, but talk about no differences in quality of life.

DR. BHATNAGAR: My name is Vishal Bhatnagar.

I'm Associate Director for Patient Outcomes at the FDA. Thank you for asking.

I'd like to talk about no difference in global health status and why that's not a measure of tolerability. Overlapping curves of global health status, I just want to unpack that. What is global health status as measured by the EORTC QLQ-C30? It's two questions, asking patients on a scale of 1 to 7 to rate their quality of life and their overall health. Well, if the toxicity is anemia and the symptom is fatigue, then there are ways in this current modern era to assess that using specific purer measures that look at anemia-specific symptoms.

So I think asking patients these two big questions and presenting overlapping curves, and asking patients once a month those two big questions, may not be a direct assessment of the impact of anemia and fatigue. I do want to make it clear that overlapping global health status is not a measure of tolerability, whether it's anemia or the symptoms that you just asked about, Dr. Madan.

DR. SPRATT: Okay. Thank you.

We're going to do one more from our patient representative.

Terry?

MR. KUNGEL: I want to go to CS-8. My name is Terry Kungle. I'd like to go to the applicant's CS-8 slide, and it goes to the whole question of toxicity. The representation that there's, essentially, no difference is very troubling to the patient community. And I think if you look at discontinuation, 8 and a half percent versus 1 and a half percent; dose reductions, 44 and a half percent to 1 and a half percent; dose interruptions 46 to 2 percent, you're looking at very significant differences in terms of what the patients are experiencing.

The last point is, if you know the guy's on enzalutamide just by itself, that is a really, really difficult drug to endure. And we're loading on top of those patients significant additional adverse circumstances.

DR. KENNEDY: I'd like to ask Dr. Agarwal to

the podium to --

DR. SPRATT: Real quick. There wasn't a question. What's the question?

MR. KUNGEL: So the question is, how do you reconcile saying that there's no material difference.

(Background interference.)

DR. SPRATT: Real quick, Terry.

Tom Remenick that's online, if you could mute, that would be much appreciated. Thank you, Tom.

Sorry, Terry. What's your question?

MR. KUNGEL: The question is, how do you reconcile these enormous differences with the representative statement that says, well, there's really no meaningful difference?

DR. KENNEDY: So I think you're referring to no clinically meaningful difference, which meets the 5 to 10-point threshold in global health status and quality of life, which we were not tying directly to tolerability. I just want to point that out.

I'd also like to have Dr. Agarwal respond to your question about overall tolerability.

DR. AGARWAL: The median overall survival of multiple mCRPC trials, also real-world data, consistently less than 3 years, 30 to 35 months, that's what we have seen.

In this study -- and by the way, I'm talking about unselected Cohort 1, ITT population, which everything was prespecified -- if we just look at radiographic progression-free survival with enzalutamide plus talazoparib, that is almost 14 months longer than the median progression-free survival of enzalutamide, so 19 months versus almost 33 months, and that is delaying in disease progression.

We all know that when castration-resistant disease progresses, that is accompanied by symptoms which can far outpace or overrun the symptoms of these medications. So, in my view, as a clinician, when I assess the benefit of the drug, this is always the counteracting forces of the side effects of a medicine and the disease control. So I would

say, yes, these patients are living longer. They are on the drug without progressing. They are doing well for 14 extra months, 46 months of overall survival. I think it's unprecedented. In that case, these patients are getting talazoparib, an active drug, for which dose is being reduced or modified to adjust to the side effects.

So that's my take as a clinician, and I'd like to invite my colleague, Dr. Morgans. By the way, Neeraj Agarwal, Salt Lake City, Huntsman Cancer Institute.

DR. MORGANS: Alicia Morgans, Dana-Farber. Slide 4, please.

I want to acknowledge that patients requiring transfusions, dose reductions, this is absolutely meaningful to patients. This is a discussion in clinic where someone has to express, "I'm really tired. I don't feel well enough to be able to continue this, and a change needs to happen," and certainly, the lab data also is considered in this conversation.

But what I think is important also to

consider, as demonstrated on this slide, is that these kinds of conversations in this trial happened early. They happened at a time when a decision could be made to adjust the dose, perhaps provide a transfusion, as we heard as was required by protocol, but a majority of patients were able to stay on treatment and have minimal further intervention after that initial change and dose adjustment.

I think, at least in my clinical practice, that is something that happens whether we're talking about PARP inhibitors, whether we're talking about chemotherapies and dose adjustments, whether we're even talking about enzalutamide; because, to your point, sometimes enzalutamide on its own can make people fatigued, and we have to have a dose reduction of that agent as well.

So these are absolutely meaningful things to patients. But in the context of oncology care, when we can make these decisions and changes early on in the management, and then continue the treatment for a prolonged period of time, it often

is considered to be a reasonable expectation of patients that this is still a treatment that can be worthwhile. Thank you.

DR. SPRATT: Good, Terry?

MR. KUNGEL: Yes.

DR. SPRATT: Alright. Wonderful.

We will take a quick 10-minute break. It is 3:28 right now. Panel members, please remember there should be no discussion of the meeting topic during the break amongst yourselves or with any other member of the audience. We will resume at 3:38. Thank you.

(Whereupon, at 3:28 p.m., a recess was taken, and meeting resumed at 3:38 p.m.)

Open Public Hearing

DR. SPRATT: Welcome back. 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, the FDA believes that it is

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

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the industry group. For example, this financial information may include the industry group's payment of your travel, lodging, or other expenses in connection with your participation in this meeting.

Likewise, the 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.

For those presenting virtually, please remember to unmute and turn on your camera when your OPH number is called. For those presenting in person, please step up to your podium when your OPH number is called; and it's that podium there, not this podium up here. As a reminder, please speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, please state your name and any organization you are representing for the record. You have three minutes, and I will give a warning if you're going over it.

DR. BERHAUPT: I think I get five minutes this afternoon.

DR. SPRATT: I tricked you. It is five

minutes. Go for it.

DR. BERHAUPT: Excellent.

Good afternoon. I am Dr. Amanda Berhaupt, the Health Policy Director at the National Center for Health Research. We are a non-profit think tank that evaluates scientific evidence on the safety and efficacy of drugs, biologics, and medical devices. We do not accept funding from entities with a financial interest in our work, so we have no conflicts of interest. I'm a proud FDA alumna and appreciate the chance to share NCHR's concerns about the TALAPRO-2 trial at this important meeting.

In 2023, the FDA approved an indication for Talzenna in combination with Xtandi for patients with metastatic castration-resistant prostate cancer with an HR mutation. Patients in the TALAPRO-2 trial who received Talzenna and Xtandi reported a better quality of life for longer than Xtandi alone, and we applaud this progress for the indicated use that benefits patients' well-being.

An article from the National Cancer

Institute urge patients who receive this diagnosis to get genetic testing to identify inherited mutations for drugs that can target the specific alterations that drive someone's tumor, and screening for germline alterations in families. So we are here today to discuss the potential expansion of indication for use in patients without an HR mutation, representing most patients with mCRPC.

As you know, there were two cohorts in the trial. Cohort 1, or the all-comers, included everyone regardless of known or unknown HR genetic mutation, and Cohort 2 enrolled only patients with a positive result for genetic mutation. We agree with FDA's viewpoint that the study design of the trial has flaws that complicate our understanding about if and how this drug combination provides the same benefits identified for those with an HR mutation.

As we've heard, the overall survival improved for all-comers in Cohort 1, which the FDA attributed to the HRRm subgroup, and we agree.

Some patients in Cohort 1 did not know their status, as we heard, and subsequent testing indicated that many within this cohort, in fact, did have the mutation, including 68 patients or 29 percent of those unknowns were later found.

Currently, PARPi is approved only for patients with those tumor mutations. Trials of other PARPi have not supported an all-comers indication. So we again agree with the FDA scientists that data from trials of other PARPi in prostate cancer and the TALAPRO-2 trial that we were discussing this afternoon strongly indicate that the efficacy of PARPi is attenuated, if not absent, in biomarker-negative patients.

We also have safety concerns from this trial. Adding Talzenna increased hematologic toxicity versus Xtandi alone in patients with negative biomarkers. The combination also led to more incidences of high grade and serious adverse reactions, which led some to discontinue treatment and reduce dosing. Further, toxicity in patients without tumor mutations who received Talzenna and

Xtandi increased with age. This affects the risk-benefit ratio for biomarker-negative patients for whom any benefits are not statistically significant and may not be clinically meaningful.

There were also higher rates of anemia that were attributed to cytopenias, which led to 52 percent of patients needing at least one blood transfusion. And although the incidence of anemia and transfusions decreased over time, likely a result of lower dosage, the higher rate of adverse reactions can still lead to significant consequences for patients, particularly in a first-line disease setting where patients typically display minimal symptoms.

So, is the data sufficient to justify expanding the indication to include patients without HRRm?

Comparisons across trials raise questions about whether adding Talzenna to Xtandi has a favorable benefit-risk profile in patients without HRRm. While there were statistically significant improvements in radiologic progression-free and

overall survival in the all-comers Cohort 1, the study design limited the ability to examine the impact on patients without mutations. The study could not confidently answer that question, and this is important since most patients with mCRPC do not have an HR mutation.

Just yesterday, Commissioner Makary made it clear that the FDA must not approve a product unless research confirms that the benefits outweigh the risks. It is not clear that the benefits outweigh the risks for an expanded indication of Talzenna and Xtandi. NCHR strongly recommends that the applicant further research and explore whether the benefits outweigh the risks for patients without the HRRm genetic mutation. Thank you.

DR. SPRATT: Thank you so much.

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

MR. BOGNANNO: Thank you. My name is Thomas Bognanno, and I am a member of the Pfizer Prostate Cancer Advisory Committee, but I've received no

compensation or reimbursement for my comments today. I want to thank the panel members for this opportunity to speak. I'm not a clinician, and, obviously, not a researcher. I am a man living with advanced prostate cancer and, hopefully, I'm a voice for many others who are walking this path alongside their families.

Over the past several years, I have had to face this disease head on. Like hundreds of thousands of other men living with prostate cancer, I've dealt with many of the various options that are available today to treat this disease. That can include surgery, radiation, chemotherapy, hormone therapy, and emerging treatments that are coming today. Each one of these has its own physical and emotional tolls.

I can tell you this journey has tested me, but it's also given me perspective, and that's what I want to share with you today because, most importantly, it's given me time. And thanks to the advances in cancer research and drug development over the past decade, I've been able to not just

live longer, but I've been able to live better. I've had more holidays with my wife, I've had more birthdays with my adult children, and I've had more mornings when I can simply wake up and feel hopeful about the day ahead.

So let me be clear, this journey is not one that I've walked alone. My wife has carried so much of this burden with grace and strength. My adult children have stood by me through the many appointments, the side effects, and the long periods of waiting.

Cancer is just never one person's diagnosis. It touches everyone in the family. So today, when we're talking about new treatment options, we're not just talking about medicine; we're talking about giving families like mine more time together. We're talking about preserving moments that turn into memories that matter most. That's why giving patients like me more choices and ensuring broad access to those options is so essential. Patients like me, and so many other men facing this disease, deserve the chance to benefit from the promise of

innovation and research.

The proposed combination of these two drugs could represent something very powerful for patients like me, especially those facing metastatic castration-resistant prostate cancer. At this stage, every treatment option counts. Every delay in progression, every extension of survival, is a gift.

I know from listening today, the committee will examine the data here very, very closely, but I want you to know that the idea of an oral combination therapy that can be taken at home rather than in a clinic, it isn't just medically significant to me, it's humanizing. It means fewer hours hooked up to a machine. It means fewer long drives for appointments. It means more dignity during a time when so much feels out of our control.

The committee, I know, is going to examine the data closely, but as a patient, I ask you also to consider the lived experience of people like me. The questions that should weigh most heavily, I

hope, in your decisions are, does this therapy offer real hope; hope for more time and better quality of life? When balanced against a very manageable side effect profile, is the survival benefit significant enough for patients to handle the side effects without losing their sense of self? And finally, will the people who need it most truly have access to it?

I know this. You can't ignore the equity gap when it comes to prostate cancer. Men in underserved communities, especially Black men, face higher risk and worse outcomes with prostate cancer. We owe it to them. We owe it to all patients to ensure that innovation reaches every corner of our communities and that all men have equal access to it when it becomes available.

I'm here today because I've been fortunate. I'm here today because science and innovation has kept me here. I want other men to have that chance as well. Patients, we don't want just more time; we want time that we can enjoy with our loved ones. Thank you for hearing my voice and for valuing the

patient's perspective in the decisions you're making regarding Talzenna. They matter more than you realize. Thank you.

DR. SPRATT: Thank you so much.

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

MR. REMENICK: Yes. Thank you. My name is Tom Remenick. I'm a prostate cancer patient. I represent myself, but I am a member of the Pfizer Prostate Cancer Steering Committee, and I am not receiving any compensation for this meeting.

I was diagnosed in 2010. Shortly after diagnosis, I had a prostatectomy. All was well until three years later when I experienced biochemical recurrence. The recommended course of treatment was salvage radiation and 2 years of leuprolide. Unfortunately, 2 and a half years after the radiation treatment, I had biochemical recurrence again, this time with a more aggressive rate of progress.

Failing surgery and radiation treatment, the

only course of action was medication via FDA-approved products or clinical trials. Clinical trials were explored, but ultimately I was prescribed the medication appropriate for an aggressive recurrence of the disease. While there have been some dosage changes and minor adjustments over time, I have successfully been on the same medication for 8 years. I will clearly be on medication for the rest of my life.

While it is not out of the realm of possibility, my current situation is unlikely to last. It is highly probable that the medications will eventually become ineffective. To stave off further progression, other medications will be required that have a different mechanism of action. Since there's no guaranteed cure for prostate cancer, the importance of new and better medications cannot be underestimated.

Years ago, it was estimated I would have six good years to live, and while I have certainly beaten those odds, I am keenly aware of how the disease can mutate or become resistant with

life-changing, or even life-terminating, consequences. I'm also aware of how much science has progressed, providing additional treatment options, and that is the key to my future.

For prostate cancer, progress and treatment is often measured in months, ideally tens of months, but most often less. And while that seems like a short time, I would be extremely grateful to have those additional months when the time comes; however, they must come with some quality of life. Now, that quality of life can be diminished from what I have today, and that would be certainly acceptable, but mostly, I would like to have the opportunity to make those trade-offs. It is only through new and expanded medications that I will have that opportunity; therefore, I do urge the FDA to ensure safety and approve medications for all stages of prostate cancer to inhibit the delay, progression, ultimately prolonging life, even for months.

With every new or expanded use of medication, including the research and the trials

required to bring that medication to patients, something new is learned about the cancer and its progression. So to be a little less self-serving, even if a new medication does not prolong the disease as much as I would like, or precisely provide even a diminished quality of life, I would still like to have it prescribed so my experience may contribute to better solutions in the future. Thank you for the opportunity to share my thoughts.

DR. SPRATT: Thank you.

Speaker number 4, please state your name and any organization you are representing for the record. You have five minutes.

MS. BUGLER: Good afternoon, and thank you for the opportunity to speak today. My name is Courtney Bugler, and I'm the President and CEO of ZERO Prostate Cancer, which is a partner of the applicant, but I have not been compensated for this, and we have no financial stake in its impact. I am also a nearly 20-year cancer survivor myself and a patient advocate, and I joined ZERO because of my father, who is currently living with prostate

cancer.

ZERO is the voice for the prostate cancer community. We are the nation's number one provider of prostate cancer resources, programs, and services for those at risk, diagnosed, and their families. We work for a future where early detection is possible, support is unwavering, and quality care is accessible to all.

While we are in the room today, 16 people have died from prostate cancer -- fathers, husbands, friends -- and that urgency is why I'm here today, to support the need for more options for patients with mCRPC.

Thanks to decades of research and innovation, we are in the midst of a renaissance of prostate cancer treatment. A growing pipeline of therapies offer men more options, personalized approaches, and, as Tom said, more time. But mCRPC is a turning point in a prostate cancer patient's life. It's the moment when hormone therapy stops working; the cancer is more aggressive; the options are more intense, more invasive, and more

difficult; the future becomes uncertain, and the clock ticks faster.

At ZERO, we hear from patients every single day who are navigating this terrifying chapter. We speak to these patients every day in our 150 support groups around our country, where they call our ZERO360 patient assistance line, and when they reach out to our patient programs team. And it is not just older men. Increasingly, we see men in their 40s and 50s, men in the primes of their careers, raising young children, leading businesses, and coaching Little League baseball games.

I want to tell you about Derek [ph]. Derek was diagnosed with metastatic prostate cancer at 48 years old. He has three school-age children; or Chris, who was diagnosed at 43 with a metastatic recurrence 2 years later. They are desperate for options. They're willing to discuss the risks and benefits of therapy with their doctors. They understand that all options come with trade-offs, and they're willing to accept manageable side

effects that they manage with their doctors. They are what this treatment represents, not just progression-free survival, but time, time to be present and live their lives.

This is intensely personal for me. I've lived through cancer. I've seen what scans and treatment side effects, and anxiety, and uncertainty can do to lives, and I've seen my father, as so many others, face their own diagnosis with bravery and fear.

And I want to be clear that every data point in this discussion is not just data. It is not just elegant science on a slide. They are people, a man with a family, with dreams, and with people who love them. And that 8.8-month overall survival improvement, that is not just modest. That is a school year, that is walking your daughter down the aisle, and that is meeting your first grandchild.

For men with mCRPC, especially the more than 70 percent who don't have these mutations and currently don't qualify for targeted therapies, this could be the difference between one more

summer or none at all. We understand the need for rigor, and we respect that process, but I ask you to consider this. In a first-line setting when patients are stronger and have the most to gain from effective therapy, and almost as significant, when this combination of therapy has delayed the time until patients need to accentuate and accelerate to a more intensive option, let's be clear, this quality of life is important. And I'd like to respectfully submit that patients reporting quality-of-life outcomes is always relevant to this discussion.

The men we serve at ZERO do not have time to wait for future analysis. They are asking, "What else can we do?" And I'm asking you to consider these options. Thank you for your time.

DR. SPRATT: Thank you so much.

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

MR. AMES: Hello. My name is Harry Ames. I live in Logan, Utah with my wife Susan. We'll be

celebrating 61 years together on June 4th. This is a happy day for me, as it's my 81st birthday, and I'm delighted to be able to tell you that I'm still alive and doing well after a prostate cancer diagnosis 29 years ago. I apologize that I can't look you all in the face, but I have no teleprompter here, and my brain doesn't memorize things like it used to.

I'm not a medical doctor, but I am a rocket scientist, so if there's a lack of medical precision in my presentation, I apologize. Oh, by the way, I should state, no, I have no financial investment in anything here at all. I represent the Ames family.

My family and I express our gratitude for the wondrous work going on in our nation to control or defeat cancer. I particularly thank the FDA and their pharmaceutical partners, physicians, and specialty hospitals that are working miracles to quell the vicious deeds of prostate cancer cells.

My cancer journey began with the discovery of moderately aggressive prostate cancer. I chose

nerve-sparing radical prostatectomy as the best solution for me at that time. That worked well for many years, but then my PSA began to climb precipitously. So I contacted the Huntsman Cancer Institute, and there I had a bladder tumor surgery followed with pinpoint radiation. Soon after that, the PSA began a new climb that resulted in a diagnosis of metastatic cancer.

I was placed under the watchful eye of Dr. Neeraj Agarwal at the Huntsman Cancer Institute. I was on a short-term drug trial that, though appearing to work for me, was not considered effective across the spectrum of others on that trial, so it was canceled. Dr. Agarwal then submitted my name as a possible candidate for a double-blind trial of the drugs being considered here for standard of care for men with my form of cancer.

Thankfully, I was accepted, and that was about 5 years ago. My PSA has remained undetectable for the duration. In consultation with Dr. Agarwal and considering my age, I chose to

withdraw from the trial 6 months ago to give my body a rest. My wife and I felt very good about suspending the trial, and I'm enjoying some improved energy since withdrawing. Dr. Agarwal continues to be my guardian angel, keeping watch every few months to make sure I'll have no scary surprises.

The trial drugs themselves had little overall negative effect on my quality of life, other than providing me a life in which to have quality. The only bothersome part of the treatment is the all important and necessary and miserable androgen suppression. I hope that one day there will be a new pill that will provide a testosterone replacement that has all good effects but is hated by prostate cancer cells. That would be a golden and glorious day.

When I was first diagnosed, I strayed on to the internet to discover all I could about the condition. There I read some worrisome mortality numbers. You see, I was looking forward to a future of marriages, grandchildren, great

grandchildren, and graduations from high schools and universities. I was convinced after seeing the mortality figures that I wouldn't get the chance to experience those wonderful things. As it turns out, in just the last 5 years of the recent trial with this candidate drug, eight great grandchildren have come into my life, and there have been many other wonderful family events.

I come before you today as a totally fulfilled man. If I should pass tomorrow, the life that has been given me in the past 5 years is enough. May God bless all members of the great teams who've given me these past precious years.

DR. SPRATT: Thank you, sir, and happy birthday.

MR. AMES: Thank you.

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

I'm going to ask if there are further clarifying questions, and if not, we will go to the discussion.

(No response.)

Questions to the Committee and Discussion

DR. SPRATT: Wonderful.

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 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.

After I read each question, we will pause for any questions or comments concerning its wording. We will proceed with our first question, which is a discussion question.

Are there any questions related to the wording of this?

Dr. Vasan, do you have a question about the wording? No. Okay.

I see no questions, so we will proceed with our first question. If there are no further

questions or comments concerning the wording of the question, we will now open the question to discussion.

Dr. Vasan?

DR. VASAN: Neil Vasan. I think this is a very, very important question that is critical for not just prostate cancer, but all cancers. And I think that we have some historical examples. We've seen this story before, but I also think we have the tools to operationalize this very important question.

The trial that I kept coming back to when I was reading the FDA and the applicant's information was NSABP B-31, which was the pivotal adjuvant trastuzumab trial in breast cancer. There were retrospective analyses that looked at patients with HER2-low, what we now call HER2-low breast cancer. And in these retrospective analyses, the hazard ratios were very, very striking for both disease-free survival and overall survival. There was a lot of preclinical data, and this led to the hypothesis that HER2-low would predict for adjuvant

trastuzumab efficacy, but when this was tested prospectively, this was a negative trial.

But then, what's fascinating is that, then, years later, with DESTINY-Breast04 testing trastuzumab deruxtecan, this is where we took that biomarker that didn't work before, and it spurred innovation to find a new therapy that works in that population.

So I think this sequence underscores a very important regulatory and historical pattern, where testing, formally, drugs in a biomarker-negative population not only answers the question, but it also spurs discovery to finding therapies that work in that population. So that's the first point I wanted to discuss.

The second is that I think that this is a very interesting question now in 2025 compared to, let's say, 10 years ago because companion diagnostics have completely changed how we can test for biomarkers in patients. They are much faster now. They're much more comprehensive with gene panels. They're much more sensitive. They're much

more patient friendly with liquid biopsies, and they're much cheaper.

I think we've seen several clinical trials recently that have resulted in FDA approvals. I'm thinking INAVO120 for inavolisib, there were 93 percent of patients enrolled based on ctDNA. That is an incredible advance that we didn't have 10 years ago. So I think that we can not only address this academic question, but also operationalize it. I think we have all the tools in the field to do so. Thank you.

DR. SPRATT: Dr. Graff?

DR. GRAFF: Julie Graff, OHSU and Portland VA. So this is just the discussion point, but I would like to bring up some of what people say. When it comes to treating men with a certain mutation in the PROpel conversation, and also in this conversation, the question comes up, well, some patients don't have access to sequencing, so therefore, there might be some patients who miss out on this medication because they were never tested.

For those comments, I would like to say I disagree with the idea of just treating them anyway, and I would highlight, too, that everyone should be sequenced because HRR mutations are not the only important ones that can lead to treatment. Other ones such as microsatellite instability are also important. Thank you.

DR. SPRATT: Dr. McKean?

DR. McKEAN: I would echo that, actually. I realize, coming from the community oncology setting, that we have a lot of room for improvement to adhere to the recommendations for biomarker testing so that we can truly be confident that we're finding the patients that will benefit from biomarker-driven therapy. And yet, we look into the community to a well-done clinical trial, that's designed well, where the patients are tested, as they should be, so that we can be confident of the results from a statistical perspective and efficacy perspective. Thank you.

DR. SPRATT: Dr. Gradishar?

DR. GRADISHAR: Yes. I was just going to

amplify some of the comments -- Dr. Gradishar, Northwestern -- that Dr. Vasan just mentioned.

If you look at the example of T-DXd, or trastuzumab-deruxtecan, which is seemingly a panacea for just about everybody with breast cancer, seemingly, we could in the guidelines say that. But we obviously don't because we want to restrict it to where we have clear evidence that it's helpful. And part of that is driven by biomarkers, which are imperfect, and that's also countered by the fact that we recognize that there's significant toxicity in a population of patients. So though the drug is very effective, we want to be very sure that we're treating the appropriate patient population with the drug.

So I think that mirrors part of the discussion we're having here. I would want to be very confident that we're treating the right patient population with the drug in question today.

DR. SPRATT: Thank you.

Any other discussion points? May I call on you, Dr. Madan, as a prostate specialist?

DR. MADAN: Ravi Madan, National Cancer Institute. I just want to say that the toxicity dimension here is a big part of this conversation. I don't think we'd be at an ODAC if this was a non-toxic component to the method of management. Just because grade 3 and 4 toxicities are heme or, quote/unquote, "manageable," they still can impact patients in ways that probably it's hard for us to fully understand with our questionnaires and things. And I do think that the impact on appetite by nausea and decreased appetite in cancer patients is especially important. I think that's where it becomes challenging.

Then there are questions about the statistical planning and even the relative trends that we're seeing here. So I think the safety part, which is very patient-centric, is really at the heart of all of this. Thank you.

DR. KENNEDY: [Inaudible - off mic.]

DR. SPRATT: The applicant doesn't speak unless we call upon you in this section here.

DR. KENNEDY: There was a question that we

had before the break that --

DR. SPRATT: Oh. Go for it. What was the question?

DR. MADAN: Ravi Madan, National Cancer Institute. I asked for the breakdown of nausea and and anorexia. They said that they'd get it after the break. It's up to the chair.

DR. SPRATT: Sure. You want to quickly show the slide?

DR. MADAN: It's up to the chair.

DR. SPRATT: Go for it.

DR. KENNEDY: Thank you. Dana Kennedy, Pfizer Oncology, GU Development Head. Slide 1 up, please.

In response to your specific question on grade 1 versus grade 2, nausea and decreased appetite, what we're showing here is the combination arm compared to placebo plus enzalutamide. We see that the majority of adverse events for nausea and decreased appetite are grade 1 with a lower incidence of grade 2 events. We also see the same pattern for enzalutamide with

more grade 1 events versus grade 2, and relatively modest differences between the two groups.

DR. SPRATT: Thank you so much. Appreciate it. You got your brownie points back.

Mr. Tendler?

MR. TENDLER: Craig Tendler, industry representative. Just regarding the discussion point, I think, for me, no question; you want to see what the efficacy and benefit-risk profile looks like in a formal biomarker-negative population. I think it's also important to clarify what efficacy means because I think as we see more and more effective agents in the salvage setting -- and of course this was also brought up in the discussion today -- it becomes harder and harder to show an overall survival advantage.

So as long as efficacy can also be demonstrated with other relevant endpoints in this setting -- and we've heard from many of the patients as well, whether it be quality of life, whether it be time or prolongation, or time to symptomatic progression, time to cytotoxic

chemotherapy -- I think these are all very relevant endpoints in this setting, specifically of castration-resistant prostate cancer, and should be considered as part of an efficacy evaluation.

DR. SPRATT: Mr. Kungel, any comments you have?

MR. KUNGEL: So, let me start by saying -- my name is Terry Kungle -- I got involved with PARP back in 2016. There was a very good friend, Stu Hunter. He had basically failed every treatment there was, and he was a guy that was out of luck and out of options. And at the last moment, Dana-Farber, they got him on olaparib, and he had an absolute huge quality of life for an extended period of time.

So I've been following PARP for 10 years and have gotten enormously excited over the years about PARP. But it's been a continuing series of frustrations in terms of you think you've got it, and then you don't. You look at the PROpel and MAGNITUDE trials, and you come away saying, I would love to see this expanded, but unless we really

know where it's going to work and who it's going to work, we've got to get back to the right patient, right treatment, right time, and I don't think we're there yet with this situation.

I would say there's a problem with the clinical design, and it got to the point, for me, the only thing I could read and make sense out of was the double negatives. And then you started to look at that data relative to Cohort 1, and you started to see some very clear differences. So I do think that there's a very big question out there for me in terms of whether or not there -- the benefit is reduced and the toxicity issues are pretty big.

There's also a question of, if you look at what we're doing with patients today, the cost of enzalutamide is not low. You add on the cost above that, and you're looking at not only toxicity in terms of medical care, you're also looking at enormous financial toxicity. I come from Maine. We have the oldest age population in the country, and we're beating Arkansas and Mississippi in terms

of per capita income, but not by much.

DR. SPRATT: Thank you.

The way I look at this -- oh. Dr. Pazdur, go for it.

DR. PAZDUR: One of the things I want to emphasize -- and I'm speaking from personal experience having buried family members that have faced similar dilemmas and multiple family members buried -- patients have a right to know what they're getting into, what the expected benefit is going to be. They're signing up for toxicity.

I think if you have a marker-positive and marker-negative populations, people know that. So they want to know, if I was marker positive, what's the effect of this going to be? And I could weigh the benefits of this therapy. If I'm marker negative, what's the benefit? If it's minuscule, maybe I don't want to go on this therapy. And if it's indeterminate, let's perhaps do another biopsy, getting to Craig's issue of the practice of medicine. I'll go through another biopsy. I'll go through three biopsies. If a therapy is going to

be given for 2 years, or whatever it is, I want to know what that benefit is going to be.

I think they have a right to get that information. And I just want to emphasize that we as a federal agency have to protect the patients' rights here, and people have a right to know what they're getting into when they have these therapies being prescribed to them.

DR. SPRATT: Thank you.

Dan Spratt, UH Seidman and Case Western Reserve University. So I think stating it a little bit differently, actually, when you have a predictive biomarker -- and to be very clear, and I'm not going to ask the applicant, but I would expect them to say that BRCA and HR mutations are predictive biomarkers -- there is differential benefit even in TALAPRO-2.

So we as a field have a predictive biomarker. I actually don't think that you should conduct a trial with an unknown biomarker status. I think that you should be doing it always prospectively with a biomarker-negative and/or

positive status to test the hypothesis if there's maybe this benefit in biomarker-negative patients.

I think as we've seen today, in the single mutation, or the single test group, the curves actually looked worse early on, but the hazard ratio, despite it violating proportional hazards, was basically 1. It was 0.99. So in the real world, you're going to usually get one test. So do I use this trial to say you're going to have potentially worse, no benefit in survival, or is that post hoc and a spurious result? Do I say the undetermined status, which has a hazard ratio greater than 1, just over, is that spurious or is there no benefit in that? It's a very slippery slope to, then, pick out the group you end up wanting to look at.

And although I'll say I respectfully disagree with Dr. Pazdur, I would say that the magnitude to me matters because if the RMST benefit is 0.2 months, ignoring all p-values and anything of that, that's about a week. So are we going to give all the toxicity and the cost -- I know the

FDA doesn't factor that in, but it's in a paper and in ASCO. It was three-quarters of a million dollars when they compared it --

Terry, you can --

MR. KUNGEL: It was $727,000.

DR. SPRATT: So that's in the real world, not on a trial. That is a cost to a patient.

So I think going forward, if the companies still want to be evaluating in the biomarker-negative space, I think they and experts, which is not me, on the diagnostic side -- because I think there are also limitations of these tests such as liquid biopsies. I think, for example, BRCA2 deletions don't have a great frequency of detection. The tumor content -- for example, doing these tests after treatment has started -- can have false negatives. I think it is critical.

DR. PAZDUR: How can I not clarify my statement? What I was talking about, really, is the comment where people say the effect is so big, it has to be real. And that's the point I was trying to make. You can't use that analogy, and we

have seen that on numerous occasions here.

One particular example -- in fact, we were going to include it in our presentation and we took it out -- was one of the drugs that we removed after giving it accelerated approval. The accelerated approval was based on a PFS, but the overall survival in this sarcoma study was over a year. It was not alpha controlled, poor statistical design, but it was a finding that was descriptive. When a randomized trial was done, there was no difference in overall survival at all, no difference.

So the importance is this is not just a pin-headed issue of statistics. It's really where the rubber meets the road of having these things prespecified.

DR. SPRATT: Thank you.

This is Dan Spratt, UH Seidman, Case Western. I intentionally didn't pin the applicant to this, but there is quite a bit of data. Only, I think, one of the companies with an FDA-approved PARP inhibitor has published it that I've seen, is

the difference in mono and biallelic loss. I haven't seen it with this data.

You have one of the best assays, best trials, best first author of the paper, best PI. It would be great to understand the mechanism. If this whole phenomenon of an ARPI with talazoparib induces this state, do we still see this difference in mono versus biallelic? In the paper, in Nature Medicine, why with ATM, still? With ATM cluster, the hazard ratio is 0.9.

So anyways, there are just a lot of questions, so I think this is important.

So moving on, unless there are any other discussion points from the panel.

Dr. Graff?

DR. GRAFF: Julie Graff, OHSU, Portland VA. I don't know if this is an ok comment, but you can let me know. I've heard so many passionate comments from patients and patient advocacy groups, and I would say, in addition to that, why not demand a good clinical study? Instead of wanting the medication because of the results of a study

that wasn't positive, or didn't really convincingly show that it helped, why not do another study with just the people you're interested in?

DR. SPRATT: It seems like a fair comment.

Any other comments? Dr. Vasan?

DR. VASAN: Neil Vasan. This discussion of formally testing biomarker-negative patients I think is very important. This wasn't part of this application, just to be clear, but we've had other PARP inhibitors where in the biomarker-negative population, there were decrements. There were decreases in some of these endpoints. So we have to be formally testing these and, hopefully, not trying to ascertain this in some sort of ad hoc way.

I also recognize that I think that the PARP inhibitor field has changed, and this trial did integrate prospective testing, which I think is notable, and the applicant should be commended on that. Some of the prior PARP inhibitor trials, it was all retrospective, so this is very helpful for the field. Thank you.

DR. SPRATT: So to summarize the discussion, the applicant should be commended for conducting a well-designed trial, for doing prospective testing, and probably the best trial to date that's been done in this setting. However, despite that, it still was not truly designed and powered to assess the biomarker-negative subgroup, and a lot of questions arise regarding the true biomarker-negative subgroup; do they benefit, do they not benefit?

I think other points that were raised were concerns regarding toxicity, potentially financial toxicity. But the actual toxicity to patients, the question was raised, why not demand that there is formal statistical testing and formal trials for this subgroup of patients so that if it was positive, this could reach patients all across, potentially, the world, not just the U.S.?

MR. KUNGEL: This is Terry Kungel. May I just add one quick other comment to the applicant? I was really intrigued by 2.4.3, where you're talking about the 33 feature, 3 gene,

3 transcriptions, signatures. That looked to be, for the patient community, something that could be enormously exciting and interesting.

DR. SPRATT: Thank you.

I will add that the gene expression signature, the signature that he references, would be very exciting to learn more, potentially deploy, validate further, and get to patients. Maybe that's what's needed to get this, and to expand what a functional HRD means beyond simply alterations. And then I'll make the plug, it would be great if you present the data or publish it on mono versus biallelic, now that that's on the record.

So, we will now proceed to question 2, which is a voting question. We'll be using an electronic voting system for the meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may

press the corresponding button until the vote is closed.

After everyone's completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to. We will continue in the same manner until all the questions have been answered or discussed.

For question 2, are the results from TALAPRO-2 sufficient to conclude a favorable benefit-risk profile for adding talazoparib to enzalutamide in patients with non-homologous recombination repair mutated metastatic castration-resistant prostate cancer?

Any questions to the wording of this?

(No response.)

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

question, we'll now begin the voting process. Please press the button on your -- microphone. I don't call this a microphone, but it's ok. I'll talk to the FDA later about that.

MR. KUNGEL: Sorry.

DR. SPRATT: No, I appreciate it. I need help often.

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

(Voting.)

DR. SEO: This is Jessica Seo, DFO. For question 2, the results are as follows. There were 0 yeses, 8 nos, and 0 abstentions.

Dr. Spratt?

DR. SPRATT: Now that the vote is complete,

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

We'll start with Dr. Gradishar.

DR. GRADISHAR: Bill Gradishar, Northwestern. Not to relitigate the entire discussion, but just to emphasize that there was concern on my part, as well as many others, about full characterization of the non-mutant population, the statistical assumptions that went into making the case that there was a benefit. And I think the toxicity data really demonstrated that oncologists can take care of toxicity. It didn't really necessarily get to the patient experience with the doublet. So for all those reasons, I voted no.

DR. VASAN: Neil Vasan. I voted no. I think that testing whether biomarker-directed therapy works in patients without the biomarker is a very, very scientifically valid question, but because it's a counter-hypothesis, it just demands a high level of rigor. Because this study was not

powered to test efficacy in the patients without HR mutations, I thought this weakened the strength of the conclusions that we can draw.

I will say that I think this is just such an important question across all oncology, and as a field, we need to commit to formally evaluating whether targeted therapies benefit patients with and without the biomarker. I know the FDA has draft guidance on biomarker testing for companies, and I hope that the discussion today helps inform newer versions of that document. This is important not just in prostate cancer, but across all tumor types, and I think just simply put, precision oncology demands precision trials.

DR. SPRATT: Thank you.

Dan Spratt. As a prostate cancer clinician and as a radiation oncologist -- and I voted no for the record -- I've treated thousands of men, and about half of the patients we treat with radiation for palliative intent near the end of life. We heard a lot of speakers today and very passionate, and I resonate with it greatly. I can think of

many patients right now that text me weekly or regularly that have metastatic CRPC that are looking for more options.

One of the tough things that I think the FDA and everyone here has to balance is that more doesn't equal better for a patient. And when I look at this, knowing there'll be difference of opinions, when I see this, I see in the overall population of non-HRRm, you have 8 out of 10 patients that had grade 3 or higher toxicity, 4 out of 10 patients needing a transfusion.

In the real world, over half of patients are over 75. In those patients, as it was said by one open public hearing speaker, the toxicities and the tolerability was substantially worse, and that is a huge majority of the men we see. The quality of life, while imperfect, was numerically worse. It was not better. So these men are not experiencing life, obviously, at least a total group, better, while there clearly will be outliers that may.

The other part we look at, does it help men live longer? As I already went over, I have great

concerns. Like I said, the single negative or the undetermined, the hazard ratio is 1, and I already went over the preclinical evidence. I'm not sure that that's even there. I think this population, while this may seem like a hit or negative to the patient community, this is a rapidly diminishing population that has not already had ARPI exposure in the mCRPC space, as well as when you factor in the patients that are eligible and tolerable, to be able to get this dual therapy.

So I encourage and I want to commend the applicant. They've done a fantastic job with this trial. I think this has had a major effect. It's unprecedented, this combination in the HR mutant population, but this is my rationale. Thank you.

MR. KUNGEL: This is Terry Kungel. I voted no. And without reiterating a lot of the comments that have been made, essentially, the choices were based on design study, the history with PARP, the toxicity, and the fact that we're trying to address 70 percent of the entire prostate cancer population.

DR. CONAWAY: Mark Conaway. I voted no. The lack of prespecification gave me pause about the robustness of the efficacy results, and in light of that, seeing the additional toxicity made me vote no on the favorable risk-benefit ratio.

DR. MADAN: Ravi Madan, National Cancer Institute. I voted no. Unfortunately, the clinical data from the TALAPRO-2 study do not really support the combination of enzalutamide and talazoparib in patients without an HRR mutation, whoever have mCRPC. I think some of the suboptimal sequencing of therapies contributes to, really, our ability to interpret the real potential benefit in the U.S. in 2025 when there's multiple subsequent therapies available for patients beyond the first-line ARPI.

Again, the toxicity can't be ignored here. Just because we can manage a toxicity doesn't mean it doesn't impact patients' lives. Even if we warn them about it ahead of time, sometimes that's maybe even worse. The other thing is, even grade 1 and 2, nausea and anorexia, are important, especially

in cancer patients where nutrition quickly becomes an issue.

One other thing we must acknowledge about where prostate cancer is in 2025, and is headed, is, really, the adoption of ultra-sensitive, next-generation imaging such as PSMA. I think we have to acknowledge that this is leading to a form of stage migration, whether some of us like it or not. And this is leading to earlier diagnosis of metastatic disease, or at least what's being called metastatic disease, and that will lead to an earlier diagnosis of mCRPC or what's being called that.

So this adds a further dimension to the potential for overtreating patients and exposing them to toxicity with an ARPI and a PARP inhibitor without insufficient statistical support from the clinical data.

I do want to thank the sponsor, Pfizer, FDA, and the open mic speakers for their contributions and continued efforts in dealing with prostate cancer and improving lives for men with prostate

cancer. Thank you.

DR. McKEAN: Heidi McKean. I voted no. Remembering metastatic castration-resistant prostate cancer is an incurable cancer at this time, is intervening with an additional potentially toxic drug beneficial to the patient? And I would have to say that without a clear statistical plan to prove efficacy for these non-HRR-mutated patients, we just don't know from this data set.

DR. GRAFF: Julie Graff. I voted no. I agree with the other sentiments. I would add that this group in this room is responsible for drug approval, and we're setting the stage for other people in the community who don't treat prostate cancer day in and day out. So while we might understand the data very well, there might be someone, a general oncologist somewhere, who doesn't, or a urologist. Many people can prescribe these drugs, so it's important that we make the right decision.

DR. SPRATT: Thank you so much.

I do want to echo what's been said and thank

both the FDA, as well as the applicant and all of our speakers. Before we adjourn, are there any last comments from the FDA?

DR. PAZDUR: Just to thank all the committee members for the past two days? I know it's been a long two days, and we really appreciate all your efforts here on all of the four ODACs.

Adjournment

DR. SPRATT: Thank you so much.

We will now adjourn the meeting. Thank you so much.

(Whereupon, at 4:39 p.m., the afternoon session was adjourned.)