FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Tuesday, December 17, 2019

Afternoon Session

1:00 p.m. to 4:36 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(1:00 p.m.)

Call to Order

Introduction of Committee

DR. HOFFMAN: Good afternoon, and welcome back to some. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you've not already done so. I would also like to identify the FDA press contact, Brittney Manchester. Would you stand for a moment? Thank you.

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

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

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

DR. SUZMAN: Daniel Suzman, clinical team lead.

DR. BREWER: Jamie Brewer, clinical reviewer.

DR. CHENG: Joyce Cheng, statistical reviewer.

DR. APOLO: Andrea Apolo, medical oncology, NCI, chief of the bladder cancer section.

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

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

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

DR. HOTAKI: Lauren Hotaki, designated federal officer.

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

DR. CRISTOFANILLI: Massimo Cristofanilli, breast oncologist, Northwestern University, Chicago.

DR. ULDRICK: Thomas Uldrick, medical

oncology, Fred Hutchinson Cancer Research Center.

DR. HAWKINS: Randy Hawkins, private practice, Charles Drew University, medicine and science.

MS. JOHNSTON: Colette Johnston, patient advocate.

DR. PAVLOVICH: Christian Pavlovich, urologic oncologist, Johns Hopkins.

DR. AGARWAL: Piyush Agarwal, urologic oncologist, University of Chicago.

DR. SIDDIQUI: Minhaj Siddiqui, urologic oncologist, University of Maryland.

DR. MURDOCK: Jonah Murdock, urology, Washington D.C., VA Medical Center.

DR. KRAUS: Albert Kraus, industry representative, Pfizer Corporation.

DR. HOFFMAN: Thank you.

For topics such as those being discussed at today's meetings, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that

individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

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

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

Conflict of Interest Statement

DR. HOTAKI: The Food and Drug

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

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

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is

determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

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

During the afternoon session, the committee will discuss supplemental biologics license application 125514/066 for Keytruda, pembrolizumab, for injection submitted by Merck Sharpe and Dohme

Corporation. The proposed indication of use for this product is for the treatment of patients with BCG unresponsive high-risk, non-muscle invasive bladder cancer with carcinoma in situ, with or without papillary tumors, for ineligible or have elected to not undergo a cystectomy.

This is a particular matters meeting during which specific matters related to Merck Sharpe and Dohme's supplemental BLA will be discussed. Based on today's agenda for the meeting and all financial interests reported by committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. Dr Sung has self-recused from participating in this session of the meeting.

With respect to FDA's invited industry representative, we would like to disclose the Dr. Jonathan Cheng, the standing industry representative, has self-recused from participating in this session of the meeting. The alternative industry representative, Dr. Albert Kraus, is participating in this meeting as the non-voting

industry representative, acting on behalf of regulated industry. Dr. Kraus' role at this meeting is to represent industry in general and not any particular company. Dr. Kraus is employed by Pfizer.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they may have had concerning the product at issue. We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. HOFFMAN: We will proceed with FDA's introductory comments from Dr. Daniel Suzman.

FDA Opening Remarks - Daniel Suzman

DR. SUZMAN: Good afternoon. My name is Daniel Suzman. I'm a medical oncologist and the FDA team lead on this application. I'll make a few introductory comments regarding the FDA's position on the application and the issues we would like the committee to consider.

The applicant is seeking indication for pembrolizumab for the treatment of patients with high-risk, non-muscle invasive bladder cancer, or NMIBC, that has recurred or remained persistent after adequate treatment with intravesical BCG. These patients are at high risk for progression to muscle-invasive bladder cancer and ultimately from dying of metastatic disease. The standard of care for these high-risk patients is radical cystectomy if they're eligible for the procedure. However, there is a significant proportion of patients who are either ineligible for or not willing to undergo cystectomy.

Non-muscle invasive bladder cancer represents about 75 percent of new bladder cancer

cases and is generally stratified based on stage, grade, histology, and prior therapy into low, intermediate, and high-risk groups that reflect the risk of recurrence or progression to muscle-invasive or metastatic disease. High risk non-muscle invasive bladder cancer carries a particularly poor prognosis with at least a 20 percent risk of progression to muscle invasion and 14 percent risk of death from bladder cancer, with the majority of these events occurring within 4 years.

A standard of care treatment for intermediate and high-risk, non-muscle invasive bladder cancer is intravesical BCG therapy. Following persistence of disease or recurrence after BCG, radical cystectomy is generally considered the standard of care. However, radical cystectomy is associated with high risk of postoperative complications and mortality, with 90-day mortality rates up to 7 to 15 percent in some series, depending on patient age and comorbidities and the cystectomy case volume of the

surgeon and center.

For patients considered ineligible for or who refuse cystectomy, there exist limited treatment options such as intravesical valrubicin, which has a complete response rate of less than 20 percent. Since the approval of valrubicin in 1998, there have been no new therapies approved for these patients in over 20 years.

Clinical trial design for patients with BCG unresponsive disease have been challenging due to issues including the ethics of a randomized trial given the high risk of progression to muscle-invasive disease and the difficulty with defining the BCG unresponsive population in terms of risk and adequacy of prior BCG exposure.

In response to these challenges, the FDA held a co-sponsored public workshop in 2013 to discuss the development of new therapies for non-muscle invasive bladder cancer. In 2018, the FDA issued a guidance that addressed recommendations around trial population and design. For patients with carcinoma in situ, or CIS, a

single-arm trial design is felt to be appropriate to assess therapies, as no effective medical therapies are available.

The primary efficacy endpoint was recommended to be complete response rate, which can only be determined in patients who have disease at study entry, i.e., those with CIS. Given that the complete response rate is essentially zero in the absence of therapy, complete responses were felt to represent activity of the therapy in question. Partial response was not felt to be clinically relevant.

Durability of complete response was also felt to be important. For patients with papillary-only disease, a randomized trial would be necessary given a complete response cannot be easily assessed in this population, and time-to-event endpoints in a single-arm trial are difficult to interpret.

Design of KEYNOTE-057 was generally concordant with the FDA guidance. It was a single-arm trial of IV pembrolizumab in patients

with high-risk, non-muscle invasive bladder cancer, with recurrence or progression of disease despite adequate prior BCG. Cohort A enrolled those with CIS, while Cohort B enrolled those with papillary-only disease. The FDA primarily evaluated patients from Cohort A, where complete response rate was the primary endpoint.

Dr. Brewer will present the FDA analysis of the KEYNOTE-057 result in more detail. The study enrolled 102 patients of whom the adequacy of prior BCG therapy could not be verified in 5 patients. Additionally, late last week and subsequent to the distribution of the briefing document, the applicant notified the FDA that a transcription error from the central pathology vendor led to one of the remaining patients with a T1 lesion being incorrectly assessed as also having concomitant CIS. We agree with the applicant's reclassification of this patient as not having BCG unresponsive CIS, and all FDA slides reflect this updated efficacy patient population.

With the removal of these 6 patients, the

FDA is considering the remaining 96 patients to be the primary efficacy population. The safety population remains unchanged. The complete response rate was 41 percent based on evaluation at 3 months. While a data cutoff of May 24, 2019 was used for all analyses of progression and safety, an updated data cutoff of September 24th was used to update only duration of response outcomes.

Nineteen percent of all treated patients remained in response at one year following their response. This corresponds to 46 percent of patients who achieved a complete response. The median duration of response was 16 months with a small number of patients remaining in complete response beyond 2 years; a limitation with the lack of random biopsies which may identify a small proportion of patients who have residual or recurrent disease despite negative visualization and cytology.

In terms of safety, we note that in contrast to intravesical therapies for non-muscle invasive bladder cancer, pembrolizumab was a systemic

therapy with immune-related adverse events. There was extensive clinical trial and postmarketing experience with pembrolizumab.

In this study, no new safety signals were identified. Three percent of patients experienced a high-grade immune-related event. No patients in Cohort A experienced progression to muscle invasion or metastatic urothelial carcinoma prior to cystectomy, however, the duration of follow-up with a minimum of 14 months from last patient enrolled, to data cutoff and a median of 24 months, may be too short to adequately characterize this risk.

While the FDA has considered complete response rate and duration of response to be meaningful endpoints in BCG unresponsive, non-muscle invasive bladder cancer, an advisory committee has not previously discussed what magnitudes would be considered clinically meaningful in the context of a systemic therapy in patients refusing or who are ineligible for a radical cystectomy. Therefore, we would like the committee to consider the following issue during

the sponsor's and FDA's presentations.

Do the observed complete response rate and duration of response represent a favorable risk-benefit profile for patients with BCG unresponsive, high-risk, non-muscle invasive bladder cancer with CIS, treated with pembrolizumab?

Lastly, the Oncology Center of Excellence is piloting a new briefing book format this year that we've entitled Project Point/Counterpoint, in which a single briefing document containing both the applicant's and FDA's position is prepared with the intent of reducing redundancy and errata, and streamlining the presentation of the clinical data. We will solicit feedback from the ODAC members at the very end of the meeting after the vote. Thank you.

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

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

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

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

We will now proceed with the applicant's presentations.

Applicant Presentation - Jeffrey Stuart

DR. STUART: Good afternoon. My name is Jeff Stuart. I am executive director and global

head of regulatory affairs for our bladder cancer therapeutics program at Merck. I would like to thank the FDA and the advisory committee members for your time. Today, my colleagues and I will present data to support the supplemental biologics application for pembrolizumab for the treatment of patients with BCG unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma in situ.

Pembrolizumab is a highly selective, humanized monoclonal antibody that binds to human program cell death 1, PD-1, and blocks the interaction between the PD-1 pathway receptor and its ligands on antigen-presenting tumor cells. Pembrolizumab is registered and approved in over 90 countries.

To date, the U.S. FDA has approved pembrolizumab for 15 different cancer types and across multiple lines of therapy. Perhaps many of you have used pembrolizumab for the treatment of patients with some of these cancers. In the urothelial cancer space, pembrolizumab is the first

and only checkpoint inhibitor to have demonstrated overall survival benefit in advanced and metastatic urothelial cancer. In addition, there is encouraging early data from studies of pembrolizumab in patients with muscle-invasive bladder cancer.

Together with the data that will be presented today in non-muscle invasive bladder cancer, it is evident that pembrolizumab has clinically significant activity in multiple urothelial cancer settings.

This diagram contains registration trials in the bladder cancer space, shown here from the least to the most invasive cancers as we move from right to left. We have an extensive development program in muscle invasive and metastatic disease. KEYNOTE-045 and KEYNOTE-052 are the pivotal trials that led to the approval of pembrolizumab in metastatic urothelial carcinoma in 2017. We have two trials in the non-muscle invasive bladder cancer space, shown on the far right.

The trial we will focus on today is KEYNOTE-

057, investigating pembrolizumab monotherapy in patients with BCG unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma in situ. In total, this illustrates Merck's deep commitment to developing and registering new therapies for patients with urothelial cancer who are in need of improved treatment options.

With our current application seeking regular approval from FDA, pembrolizumab is proposed for the treatment of patients with BCG unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma in situ, CIS, with or without papillary tumors, who are ineligible for or who have elected not to undergo cystectomy. In our presentations, we will refer to this patient population as BCG unresponsive CIS.

KEYNOTE-057 closely followed the guidance from FDA and the medical community to appropriately evaluate pembrolizumab in BCG unresponsive CIS patients. This timeline illustrates the key regulatory milestones for pembrolizumab development. Although the FDA guidance was not

available at the time of development of the study, and even before pembrolizumab was first approved by U.S. FDA in 2014 for any cancer therapy, Merck had been interacting with FDA about how to design and conduct a study in BCG unresponsive CIS patients. This includes alignment with FDA on the design of the study, selection of the endpoints, and determination of the sample size that is sufficient for evaluation of benefit-risk.

KEYNOTE-057 results form the basis of the application under review today. The marketing application was submitted in July and was granted priority review by FDA the following month. By being granted priority review, FDA determined that pembrolizumab has the potential to be a significant improvement compared to currently available therapies for the treatment of patients with this serious condition.

Here are some of the points you will hear today to support that pembrolizumab has a positive benefit-risk profile in BCG unresponsive CIS patients. There is a significant unmet medical

need for these patients who require effective alternatives to radical cystectomy, but unfortunately have no well-accepted nonsurgical options. Pembrolizumab demonstrated direct evidence of clinical benefit both in terms of a 41 percent complete response rate and by durable responses that are characteristic of pembrolizumab therapy in other tumor settings. With pembrolizumab, the window of opportunity for radical cystectomy is preserved.

The safety profile has been extensively documented across multiple tumor types with over 30,000 patients treated worldwide in clinical trials. The experience in KEYNOTE-057 was consistent with other studies using pembrolizumab. Therefore, pembrolizumab offers the opportunity for patients to experience a complete and durable response and preservation of their bladder without undue risk of cancer progression.

Here is the agenda for the rest of our presentation today. First, we will hear from Dr. Gary Steinberg who will summarize the treatment

landscape and the challenges in managing patients with BCG unresponsive CIS. Then Dr. Ekta Kapadia will review the efficacy and safety data from KEYNOTE-057. Dr. Ashish Kamat will then put this data into context and discuss how pembrolizumab can add to the armamentarium for physicians treating patients with BCG unresponsive CIS, and we will conclude with Dr. Scot Ebbinghaus who will provide an assessment of pembrolizumab's benefit-risk profile in this high-risk disease.

In addition to our speakers, Dr. Arjun Balar, a bladder-focused GU medical oncologist and Dr. Jonathan Epstein, an expert GU pathologist, are also available to help answer your questions. Now I would like to invite Dr. Steinberg to the podium.

Applicant Presentation - Gary Steinberg

DR. STEINBERG: Thank you. My name is Gary Steinberg. I'm director of the Goldstein Urology Bladder Cancer program at NYU Langone Health. I'm going to discuss the disease background and unmet need in non-muscle invasive bladder cancer and give a little context to the problem. I'm a paid

consultant to the sponsor but I have no financial interest in the outcome of this meeting.

Bladder cancer is a major health issue. In the United States, bladder cancer is the sixth most common cancer and ninth leading cause of cancer death. There will be an estimated 80,000 new cases diagnosed and about 18,000 deaths from bladder cancer in 2019. But prevalence is much higher with approximately 600,000 patients living with this disease.

Bladder cancer is generally a carcinogen-induced malignancy with tobacco smoking as the most common culprit. The pathogenesis of bladder cancer begins with chronic exposure of the bladder lining to urine concentrated with carcinogens. Thus, once cancer develops in one part of the bladder, the entire bladder and remaining urinary tract is at risk. Because of advanced age, most patients have multiple medical comorbidities such as lung disease, heart disease, and kidney disease, which is a significant factor in the safety and tolerability of treatments in

this patient population.

Non-muscle invasive bladder cancer, NMIBC, is the most common type of bladder cancer diagnosis, about 75 percent of new cases. This cancer is present in the lining of the urinary bladder but not to the muscularis propria, and the remaining 25 percent are muscle-invasive or metastatic bladder cancer.

Circled on this illustration are the different stages of NMIBC, Ti's, carcinoma in situ, or CIS, which is restricted to the urothelial lining and often diffuse and patchy in nature, and thus is difficult to fully resect. Papillary tumors present as discrete lesions and can be noninvasive noted as Ta, or can be invasive to the lamina propria, noted as T1. Papillary tumors can be fully resected. CIS and papillary tumors often occur concomitantly.

Carcinoma in situ represents 10 percent of all NMIBC cases at diagnosis. The remaining 90 percent are papillary tumors, which include Ta and T1 tumors. We use a combination of approaches to

diagnose NMIBC, including cystoscopy, which is a standard method for examining the bladder; urine cytology, which is routinely done as an adjunct to cystoscopy; and biopsies, which provide definitive confirmation of stage and grade of NMIBC.

In clinical practice, monitoring of response to therapy is based on cystoscopic examination of the bladder along with urine cytology. Biopsies are only performed on a "for cause" basis; for example, when there are suspicious findings on cystoscopy or positive cytology. Finally, CT urogram is used to diagnose disease beyond the internal visible lining of the bladder.

CIS is considered a high-risk serious disease. Why is this? CIS is a high-grade bladder cancer and has the same genomic alterations observed in muscle-invasive bladder cancer. Carcinoma in situ can occur in isolation or can present concomitantly with papillary tumors, which can display invasive characteristics. CIS is often patchy and diffuse, making complete resection difficult and the risk of recurrence high; and if

left untreated, CIS exhibits an almost 50 percent rate of progression to muscle-invasive disease within 5 years.

How was CIS initially diagnosed and treated? The standard for treatment for CIS, plus or minus papillary disease, is TURBT to fully resect papillary lesions, remembering that CIS is not fully resectable, followed by intravesical BCG immunotherapy for up to 3 years.

Intravesical BCG has high initial efficacy with initial complete response rates as high as 75 percent. However, despite high initial efficacy, responses to BCG are often not durable, and approximately 50 percent of patients will recur within one year. These patients are considered BCG unresponsive and should not receive additional BCG therapy.

CIS that fail to respond to BCG is at especially high risk of progression to more advanced disease. Since the definition of BCG unresponsive disease has recently been more stringently standardized, quantifying the true risk

of progression in a BCG unresponsive CIS population is difficult.

However, literature reports and all high-risk, non-muscle invasive bladder cancer that utilize various definitions of BCG failure indicate that progression to muscle invasive disease will occur in 20 to 40 percent of patients within 5 years, and metastatic disease will occur in up to 50 percent of individuals who progress to muscle invasive bladder cancer with death due to bladder cancer in nearly all of these cases.

Once the patient becomes unresponsive to BCG, the only standard of care treatment is radical cystectomy with curative intent. Many patients elect not to undergo radical cystectomy or they may not be surgical candidates because of their age or comorbidities. Those patients often pursue nonsurgical alternatives, which are not guideline based. These can include intravesical valrubicin, investigational agents, or more BCG.

These options lack strong evidence of benefit. Only valrubicin is approved in the U.S.,

but it is not widely used due to lack of efficacy and limited support and practice guidelines. For those patients who do not respond to alternative therapies or progress, the only option is radical cystectomy.

Although radical cystectomy is highly curative, it is a major surgery that involves complete removal of the bladder and pelvic lymph nodes. In men, it also involves removal of the prostate and similar vesicles. In women, it involves removal of the ovaries, uterus, fallopian tubes, cervix, and anterior wall of the vagina. After removal of the bladder, a portion of intestine is resected and used to form a permanent urinary diversion to allow urine to exit the body, either to an external stoma and appliance or reconstruction.

Radical cystectomy is a highly morbid surgery. Overall 90-day mortality rate is approximately 4 percent. Patients are hospitalized for 7 to 10 days if no complications, with a rehospitalization rate of 30 percent. The use of

intestine to divert the urinary stream is a major source of complications and difficult recovery.

Why? Even though bowel resection and anastomosis is relatively uncomplicated, the human body does not like urine in the GI tract. This induces metabolic acidosis, catabolism, fatigue, vitamin deficiency, loss of appetite, and significant weight loss. Overall, 45 to 70 percent of all patients will have complications, including GI, infection, cardiac, and others. Equally important is the negative impact on quality of life, sexual dysfunction, and social and emotional wellbeing.

Valrubicin was approved by the FDA in 1998 for BCG refractory carcinoma in situ but has limited efficacy and is not widely used. This trial was performed in a different era and is not comparable to the patient population or study design of KEYNOTE-057.

The valrubicin trial enrolled a heterogeneous patient population that did not meet the standardized definition of BCG unresponsive

CIS. The complete response rate was 18 percent with a median duration of response of 13.5 months, but this was measured from the start of treatment, not from the time complete response was achieved. Thus, utilization of valrubicin in BCG unresponsive disease is very limited.

So where does this leave us today? We have limited nonsurgical options for patients with BCG unresponsive CIS. In addition to valrubicin, other salvage intravesical therapies have also been studied, including mycobacterial cell wall extract, docetaxel, BCG plus interferon alpha-2b, and gemcitabine. However, most studies are retrospective, non-randomized, single institutional series in a heterogeneous patient population. Few studies have measured CR rate and duration of response in a clearly defined high-risk population of BCG unresponsive CIS patients.

The FDA and the AUA convened a workshop in 2013 to spur clinical development of new therapies in NMIBC. Importantly, a framework for the design of clinical trials in the BCG unresponsive setting

was developed, recognizing that cystectomy was the only standard of care option, a single-arm study design in a homogeneous patient population using complete response rate and duration of response since endpoints was considered appropriate.

Potential efficacy thresholds were also debated during the workshop, although these thresholds were developed in an era when only intravesical therapies were being studied in NMIBC. The International Bladder Cancer group also subsequently published potential efficacy thresholds that would be considered clinically meaningful. The first author of this publication is Dr. Ashish Kamat, who you'll hear from later today. Importantly, systemic and IO therapies were not envisioned. This workshop and additional statements have followed that led to a clear path for future drug development in NMIBC.

Importantly, this effort recently culminated in a consensus definition of BCG unresponsive, non-muscle invasive bladder cancer, which was used in KEYNOTE-057. The first step was to define

adequate BCG treatment. This was defined as at least 5 installations of an induction course, followed by at least 2 additional doses of a maintenance course or a second induction course. BCG unresponsive disease is then defined as either persistent and recurrent CIS with or without papillary tumors within 12 months of completion of adequate BCG therapy, recurrent papillary tumors within completion of six months of adequate BCG, or T1 high-grade disease after a single induction BCG course.

In conclusion, BCG unresponsive CIS is a serious disease with a high risk for progression to muscle-invasive disease. Radical cystectomy is the standard of care, but given the high morbidity and negative impact on quality of life, many patients elect not to undergo radical cystectomy or are medically ineligible. Other than valrubicin, no bladder-sparing treatment options are currently approved for patients with CIS when BCG is ineffective. There's an urgent need for novel, non-surgical therapies.

Thank you, and I would like to now invite Dr. Kapadia to the podium.

Applicant Presentation - Ekta Kapadia

DR. KAPADIA: Good afternoon, everyone. My name is Ekta Kapadia. I am a senior clinical director in oncology at Merck. I will now provide a brief overview of the pembrolizumab clinical development program in bladder cancer, and then present the study design and summary of efficacy and safety data from KEYNOTE-057.

As Dr. Stuart highlighted previously, the pembrolizumab clinical development program in bladder cancer spans across all disease stages. In advanced metastatic bladder cancer, pembrolizumab is approved globally in the first- and second-line settings based on results from KEYNOTE-052 and KEYNOTE-045.

The survival curve on the left is from study KEYNOTE-045. Pembrolizumab was the first and only checkpoint inhibitor to demonstrate an overall survival benefit in the second-line treatment of patients with locally advanced or metastatic

urothelial carcinoma. In addition, as you see on the table on the right, pembrolizumab has demonstrated clinically meaningful objective response rates and durations of response in the first-line treatment of cisplatin ineligible patients with advance to metastatic urothelial carcinoma, based on results from KEYNOTE-052.

There was a strong impetus for investigating pembrolizumab in the non-muscle invasive bladder cancer setting. This was based on the significant unmet need for development of nonsurgical therapies in earlier stages of bladder cancer; the known activity of immunotherapies such as BCG in non-muscle invasive bladder cancer; and the established activity of pembrolizumab in advanced bladder cancer.

KEYNOTE-057 was our first study that was developed in BCG unresponsive CIS. The primary objective was to evaluate the antitumor activity of pembrolizumab by evaluating the absence of high-risk, non-muscle invasive bladder cancer or progressive disease. The primary hypothesis was

that in patients with BCG unresponsive CIS, pembrolizumab monotherapy would result in a complete response rate that was greater than 20 percent.

The study design of KEYNOTE-057 closely follows the guidance put forth by the FDA and the input received from the expert medical community. KEYNOTE-057 is a single-arm phase 2 study in patients who had BCG unresponsive NMIBC, who either were ineligible for or made an informed decision not to undergo radical cystectomy.

Cohort A includes patients who had carcinoma in situ with or without papillary disease at baseline, and all the data presented today will be from patients in Cohort A. Cohort B includes those patients who did not have carcinoma in situ and is currently still enrolling.

All patients received pembrolizumab every 3 weeks for up to 2 years and underwent efficacy evaluations to assess initial complete response rate and duration of response for up to 5 years. Those patients with a continued complete response

were permitted to discontinue pembrolizumab after 18 months.

It is also important to note that if a patient had persistent or recurrent high-grade disease in the bladder or in the upper urinary tract at any time point, including at week 12, they had to discontinue from therapy and enter survival follow-up. This was an agreement with the FDA to ensure that non-responders would quickly proceed to undergo curative surgery.

Here are the key inclusion and exclusion criteria for KEYNOTE-057. All patients enrolled in Cohort A must have had biopsy-confirmed carcinoma in situ at study entry. Patients with concomitant papillary tumors such as Ta or T1 must have undergone a visually complete resection of all papillary components. Patients must also have received adequate BCG and subsequently developed BCG unresponsive carcinoma in situ. These definitions are consistent with the FDA guidance.

All patients must have been appropriately counseled about the curative potential of radical

cystectomy and must have either been considered medically ineligible or made an informed decision not to undergo cystectomy. Also, patients must not have had muscle invasive or metastatic or concurrent extravesical, non-muscle invasive disease.

The key efficacy endpoints in KEYNOTE-057 are consistent with the FDA guidance as well. The primary endpoint in Cohort A was the complete response rate of high-risk NMIBC, which was evaluated using the exact binomial method, comparing the lower bound of the 95 percent confidence interval to the historical control rate of 20 percent. This historical control rate was based on the valrubicin complete response rate of 18 percent, which as you heard from Dr. Steinberg was based on a heterogeneous patient population.

In contrast, KEYNOTE-057 enrolled a homogeneous population of patients with BCG unresponsive CIS. The key secondary endpoint was duration of response measured from the time of first documented evidence of complete response,

which, again, in most patients occur at the first efficacy evaluation at 12 weeks.

Disease assessments in KEYNOTE-057 were performed in alignment with published guidelines and in clinical practice. Importantly, central assessment of all urine cytology, biopsies, and CTUs were required. At screening, cystoscopy with presence of CIS confirmed by biopsy, urine cytology, and CTU to confirm absence of extravesical disease were required.

During the treatment and follow-up phase of the study, cystoscopies and urine cytology were required every 3 months for up to 2 years, and then every 6 months through year 5. CTUs were performed every 6 months for 2 years, then yearly thereafter. CTUs were also required more frequently in cases of suspicious cystoscopy or urine cytology.

Biopsies were required to evaluate for recurrence or progression. If a positive cystoscopy was reported, directed biopsies of suspicious lesions were required. If only the urine cytology was positive, then random biopsies

of the bladder and prosthetic urethra in males was required.

Once patients had confirmed disease recurrence, they discontinued study treatment and entered the survival follow-up phase. During survival follow-up, general disease status, subsequent therapies, and survival status was prospectively collected. Efficacy assessment data, as collected during the treatment and follow-up phase, was not collected in survival follow-up. Pathology data at the time of radical cystectomy was retrospectively collected.

I will now summarize the efficacy outcomes of KEYNOTE-057 Cohort A, which again consisted of patients with carcinoma in situ with or without papillary tumors at baseline. In Cohort A, a total of 102 patients were treated with pembrolizumab, and this represents the safety population. Of these 102 patients, 5 patients did not meet the 2018 FDA definition for BCG unresponsive disease, and one patient was misclassified to Cohort A due to a vendor transcription error. These patients

were excluded from the efficacy population. All efficacy analyses, therefore, are based on an N of 96 patients.

Key baseline characteristics are shown here. The population enrolled in KEYNOTE-057 is representative of patients with BCG unresponsive CIS. Most of the patients were elderly males with approximately 44 percent of patients being 75 years of age or older. The median number of BCG installations was 12, illustrating that most patients had received an adequate number of BCG installations prior to study entry.

Approximately 63 percent of patients had CIS alone at study entry and 37 percent had a mixed histology. Finally, approximately 95 percent of patients had declined radical cystectomy prior to study entry and 5 percent were considered medically ineligible by the treating physician.

Here is a patient disposition slide for Cohort A efficacy population. A total of 96 patients began treatment with pembrolizumab with a median follow-up of approximately 28 months. At

the time of data cutoff, a total of 7 patients were ongoing in study treatment. Three patients had completed the full 2 years of therapy on pembrolizumab and 3 additional patients had electively discontinued after 18 months with a continued complete response as allowed by the protocol.

Most other patients discontinued only in the study at the first efficacy assessment due to persistent or recurrent non-muscle invasive bladder cancer. There were no discontinuations due to muscle invasive or metastatic disease based upon study-specified disease assessments.

This table shows the best overall response, and here you can see that pembrolizumab monotherapy demonstrated a compelling complete response rate of about 41 percent that exceeds the success criterion for the primary hypothesis test. It is also noteworthy that among patients who did not achieve a complete response at 12 weeks, no patients had developed muscle-invasive or metastatic bladder cancer at the time of discontinuation from

pembrolizumab, based on study-specified disease assessments.

When we looked at complete response rates across various prespecified subgroups, we observed consistent results. Although the numbers within each subgroup are small, and therefore it is difficult to make any definitive conclusions, complete response rates in general were consistent.

Equally important to the initial complete response rate is the durability of those responses, and here we demonstrated a clinically meaningful duration of response. Of the 96 patients in the efficacy population, 39 had achieved a complete response at the first evaluable efficacy assessment. Those patients who did not achieve a complete response had to discontinue study treatment.

This curve demonstrates the duration of response among the 39 patients who initially achieved a CR. The X-axis shows the duration of CR and begins with the time initial CR was achieved, which, again, in most patients occurred at around

3 months. The Y-axis shows the percent of patients among the initial 39 who were remaining in CR. The median duration of response was 16.2 months based upon Kaplan-Meier estimates. However, it's important to remember that this, again, is measured from the time initial CR was achieved.

Among the 39 initial complete responders, 18 patients had achieved a duration of response of at least 12 months. This equates to 19 percent of the overall efficacy population who maintained a complete response for at least 12 months. When measured from the time of treatment initiation, this translates roughly to at least a 15-month response duration.

Importantly, the extended tail of the Kaplan-Meier curve is a hallmark of pembrolizumab therapy across various tumor types, and it's suggestive of durable responses amongst the responders. This swimmer lane plot portrays the durations of response in the complete responders in a slightly different way and highlights the durability of individual patient responses.

The X-axis represents time since first dose of pembrolizumab. Each bar represents an individual patient. The black circles represent the time when initial complete response was achieved. The gray bars represent complete responders, and identified with the red arrow are those responders who continued to be followed for durability. Collectively, this durability data demonstrates a significant and clinically meaningful impact and provides patients who decline, or are ineligible for radical cystectomy, a nonsurgical treatment option with durable benefit.

Pembrolizumab also did not limit the opportunity for subsequent therapies, including radical cystectomy. This table shows subsequent therapies that patients received after discontinuing from pembrolizumab. Most of the patients went on to receive subsequent therapy after discontinuing treatment, including radical cystectomy, local procedures, or intravesical or systemic therapies. Collectively, this suggests

that pembrolizumab did not limit the opportunity for subsequent treatments.

The rates of upstaging from non-muscle invasive to muscle-invasive disease at the time of radical cystectomy are reported to be about 20 percent in the literature. Pathological upstaging to muscle-invasive or non-organ confined disease at the time of radical cystectomy is a significant concern in patients with high-risk, non-muscle invasive bladder cancer and may negatively impact the potential to undergo curative surgery, as well as survival.

In KEYNOTE-057, 33 out of 36, or 92 percent, of patients who underwent radical cystectomy had no pathological upstaging to muscle-invasive disease. Only 3 out of 36, or 8.3 percent, of patients were found to have upstaging to muscle-invasive bladder cancer. Collectively, the data suggest that treatment with pembrolizumab preserves the window of opportunity for radical cystectomy in the majority of patients.

In summary, KEYNOTE-057 is a well-conducted

study that was designed with input from the FDA and is, in general, consistent with the FDA guidance. The efficacy results demonstrate a compelling 41 percent initial complete response rate in patients with BCG unresponsive CIS. This CR rate is also accompanied by clinically meaningful durability with the median duration of response of 16.2 months in the initial responders.

Among the 39 initial complete responders, 18 patients had achieved a duration of response of at least 12 months, which equates to 19 percent of the overall efficacy population who maintained a CR for at least 12 months. Importantly, the window of opportunity for radical cystectomy is preserved as evidenced by no patients progressing to muscle-invasive or metastatic disease while on therapy, based on study-specified disease assessments and a low rate of upstaging at the time of radical cystectomy.

Collectively, the data show that pembrolizumab fulfills a significant need for a treatment that produces durable responses in

patients with BCG unresponsive CIS, who are ineligible for or make an informed decision not to undergo a radical cystectomy.

I will now move on to the presentation of safety data from KEYNOTE-057. The safety profile of pembrolizumab is well characterized, based on the large clinical program that includes more than 30,000 patients who are treated in clinical trials and the extensive postmarketing experience in nearly 300,000 patients worldwide, who have received pembrolizumab.

In the coming slides, we will review the safety data from KEYNOTE-057 in the context of the pembrolizumab reference safety data set or RSD. The RSD represents the established safety profile of pembrolizumab and is the basis for classification of adverse events in the label. The RSD is composed of safety data from 2,799 patients who received pembrolizumab monotherapy for the treatment of advanced melanoma and non-small cell lung cancer.

Here you see the overall safety summary for

KEYNOTE-057 Cohort A in the context of our established reference safety data set. The safety profile of pembrolizumab in BCG unresponsive CIS is generally consistent with the established safety profile of pembrolizumab.

As you can see, the majority of AEs were low grade. Of the 26 patients with serious adverse events, only 8 had treatment-related serious adverse events per investigator assessment. Approximately 4 percent of patients discontinued study treatment due to serious AEs, and there were 2 deaths due to adverse events reported. Both were considered unrelated to pembrolizumab treatment.

The most common adverse events, regardless of causality, in KEYNOTE-057 Cohort A were generally consistent with the pembrolizumab reference safety data set, including diarrhea and fatigue. Of note, the incidence of hematuria was higher in KEYNOTE-057 compared to the reference safety data set, but this is quite consistent with what has been seen across the bladder cancer studies and is likely related to the underlying

bladder cancer and frequent local instrumentation that is required for disease assessments.

This slide provides an overall summary of immune-mediated AEs from KEYNOTE-057 in the context of the reference safety data set. The majority of immune-mediated AEs were grades 1 and 2 and managed with recommended therapies. The rates of discontinuation from study treatment due to immune-mediated AEs was low, and no deaths due to immune-mediated AEs were reported on study. Finally, no new indication-specific, immune-mediated adverse event causally associated with pembrolizumab was identified on this study.

The immune-mediated AEs reported in KEYNOTE-057 were generally consistent with the pembrolizumab reference safety data set. The most common AEs were hypothyroidism and hyperthyroidism, and all were grades 1 or 2. The majority of other immune-mediated AEs occurred in one patient each. The grades 3 to 4 immune-mediated AEs also occurred in one patient each and included type 1 diabetes, adrenal insufficiency, and a severe skin reaction.

There were no grade 5 immune-mediated AEs in Cohort A.

In conclusion, the safety profile of pembrolizumab is well characterized, based on the large clinical trial program for pembrolizumab monotherapy, as well as the extensive postmarketing experience across various indications. The type, frequency, and severity of AEs, as well as pembrolizumab immune-mediated AEs, were generally similar in KEYNOTE-057 and the reference safety data set.

There were low incidences of serious and grade 3 to 5 immune-mediated adverse events and low incidences of treatment discontinuations due to adverse events. No new safety concerns were identified in KEYNOTE-057. The majority of AEs, including immune-mediated, can be effectively managed by following standard clinical practice for immunotherapies.

In conclusion, data from KEYNOTE-057 demonstrates an acceptable safety profile for pembrolizumab in BCG unresponsive CIS and is also

generally consistent with the established safety profile of pembrolizumab therapy. Thank you, and I would now like to invite Dr. Ashish Kamat the podium to provide his clinical perspective.

Applicant Presentation - Ashish Kamat

DR. KAMAT: Thank you, Dr. Kapadia, and good afternoon, everybody. My name is Ashish Kamat. I'm professor of urology and cancer research at MD Anderson Cancer Center in Houston, Texas. I also lead the International Bladder Cancer Group, and I'm co-president of the International Bladder Cancer Network. I'm here today as a consultant to Merck, but otherwise have no financial interest in the outcome of this meeting.

What we need today is an effective therapeutic option for our patients to safely avoid, or at least delay, the need for radical bladder removal after BCG has failed them. It's important to recognize that BCG unresponsive CIS will persist and progress without effective intervention. The only FDA-approved agent, valrubicin, is not very effective and has seldom

use today, and patients just do not want a radical cystectomy.

Radical cystectomy, as you heard, is a morbid procedure, with hospital stays as long as 7 to 10 days. It has a very high complication rate, including 15 percent hybrid complications such as bowel leak and ICU admissions.

Notably, as this curve from a JCO publication highlights -- and this is a point that not many people recognize -- radical cystectomy has the highest readmission rates of all oncologic surgical procedures, higher than lobectomy for lung cancer or even Whipple procedure for pancreatic cancer.

So when faced with the possibility of losing their bladder, these are some of the things my patients worry about. They worry about body image, sexual function. They worry about quality of life. Will my clothes fit? Can I wear a suit or a dress to church? Will I be able to dance, swim, exercise, or play golf?

Patients clearly want to be cured of their

cancer, but they also want to be able to live a full and normal life; and, hence, patients just do not want to undergo a radical cystectomy and would rather try anything else. But since we do not have an effective approved therapy for this disease state, what this means is that patients are subjected to multiple procedures for recurrences and the risk of frequent anesthesia, and too many patients are ultimately referred to me only after they've progressed either to muscle invasive or, worse, metastatic disease.

This is where an agent such as pembrolizumab comes in. Pembrolizumab was studied in the highest risk BCG unresponsive CIS population, and in this notoriously difficult-to-treat patient population, it had a clinically meaningful response rate of 41 percent. Importantly, this response was durable. The median response duration was over a year at 16.2 months, and 46 percent of responders had a response that lasted at least 12 months.

Just as important, pembrolizumab allowed patients to safely delay bladder removal if they

refused surgery. Not a single patient progressed to T2 disease while on therapy; and furthermore, in patients who did undergo a radical cystectomy, the rates of upstaging to muscle-invasive or node-positive disease was 8.3 percent, which is much lower than the 20 percent that we would expect from historic controls.

Now, while we cannot say for sure that this is due to the systemic efficacy of pembrolizumab, it remains a possible mechanistic reason for this finding.

This is how I currently counsel patients who have BCG unresponsive CIS. The primary recommendation, of course, still remains a radical cystectomy. However, most patients are reluctant to undergo a radical cystectomy, and some patients just flatly refuse to consider it. For these patients, I recommend that they enroll into clinical trials.

Unfortunately, as we know, even today, most patients in the U.S. do not have access to clinical trials. For these patients, the only approved

agent we have is valrubicin, which has limited efficacy and, hence, is seldom used, which then means that these patients have to try various off-label agents such as intravesical mitomycin, gemcitabine, gemcitabine- docetaxel combinations, and even hyperthermia, which is really not available in the U.S. as a system, per se, so many urologists resort to means such as heating chemotherapy in a water bath, and then delivering it into the bladder of patients to try and calm this disease.

The bottom line is our patients are desperate for an effective alternative to radical cystectomy. The viable option for these patients who decline or not able to undergo a radical cystectomy could be pembrolizumab, which would allow our patients not only the chance to save their bladders but to do so with minimal risk or progression.

Thank you very much. Now I'd like to invite Dr. Scot Ebbinghaus to present the benefit-risk presentation.

Applicant Presentation - Scot Ebbinghaus

DR. EBBINGHAUS: Good afternoon. My name is Scot Ebbinghaus. I'm a medical oncologist and the vice president of oncology clinical research at Merck. I oversee our late-stage development programs. Merck has the industry's largest immuno-oncology research program. There are currently more than a thousand trials studying pembrolizumab across a wide variety of cancers and treatment settings.

The pembrolizumab clinical development program seeks to understand the role of pembrolizumab across cancers, and this has resulted in numerous approvals for the drug in various settings, based on clinically meaningful anticancer activity and an acceptable and well understood safety profile. Importantly, pembrolizumab has demonstrated overall survival benefit and durable responses within advanced and metastatic urothelial cancer, and is approved with both first- and second-line indications for patients with the serious condition.

As shown in the current application under review for KEYNOTE-057, pembrolizumab offers an important treatment option for patients with BCG unresponsive CIS, who are ineligible for or make an informed decision not to undergo a radical cystectomy. There's a high unmet medical need for these patients. The natural history of this disease is one that does not resolve on its own, and in fact, if left untreated, patients will eventually progress to have a higher burden of disease with muscle-invasive advanced or metastatic bladder cancer, and those are much more serious and difficult to treat.

Pembrolizumab provides direct evidence of clinical benefit for patients with BCG unresponsive CIS, as shown by a CR rate of approximately 41 percent. Importantly, these complete responses last a long time. Based on Kaplan-Meier estimates, the median duration of response is over 16 months in KEYNOTE-057.

In a landmark analysis, almost half of initial complete responders and about 20 percent of

all treated patients had responses that lasted at least 12 months from the onset of the response. This is a clinically meaningful duration of response, and many patients continue to enjoy even longer responses to pembrolizumab. These durable responses are a hallmark of pembrolizumab anticancer therapy across multiple tumor types.

There was no progression to muscle-invasive or metastatic bladder cancer while receiving pembrolizumab on KEYNOTE-057. In addition, there was a low rate of upstaging at the time of radical cystectomy. Thus, the ability to undergo a radical cystectomy is preserved should patients elect to do so.

No new safety concerns were identified in KEYNOTE-057. Collectively, these data showed that pembrolizumab has the potential to make a major impact on the treatment of early bladder cancer that has become unresponsive to BCG. The benefit-risk balance is favorable for pembrolizumab for the treatment of patients with BCG unresponsive high-risk NMIBC with CIS, or ineligible for or make

an informed decision not to undergo a radical cystectomy.

Thank you for your attention, and following the FDA's presentation, we look forward to taking your questions.

DR. HOFFMAN: Thank you very much.

We'll now proceed with the presentation from the FDA.

FDA Presentation - Jamie Brewer

DR. BREWER: Good afternoon. My name is Jamie Brewer, and I'm a medical oncologist who was the clinical reviewer for the supplemental BLA for Keytruda, referred to as pembrolizumab throughout the presentation. The proposed indication is for the treatment of patients with BCG unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma in situ, with or without papillary tumors.

The FDA review team consisted of the following members of the clinical and statistical teams, division leadership, and project management. The key issues for discussion today focus on the

risk-benefit profile of pembrolizumab in patients with BCG unresponsive, high-risk, non-muscle invasive bladder cancer with CIS. The purpose of this advisory committee meeting is to discuss whether the observed complete response rate and duration of complete response provides patients with non-muscle invasive bladder cancer with CIS, with or without papillary tumors, benefit that outweighs the potential risk associated with systemic therapy.

During this presentation, we will briefly discuss the available treatment for BCG unresponsive, non-muscle invasive bladder cancer, and discuss the key points of the FDA guidance regarding trial design for this patient population. We will review the efficacy and safety of KEYNOTE-057 and provide a summary of the FDA position.

As stated by the applicant, BCG treatment fails in up to 50 percent of patients with progression to muscle-invasive bladder cancer observed in 40 percent of patients that failed BCG therapy. Progression to metastatic disease occurs

in up to 20 to 30 percent of patients that progress to muscle-invasive bladder cancer.

The FDA agrees that standard of care in patients with BCG unresponsive, high-risk, non-muscle invasive bladder cancer is radical cystectomy. There are no generally accepted bladder-sparing alternatives, and cystectomy is a procedure associated with high morbidity and mortality that may have subsequent negative impact on patient's quality of life.

Rates of morbidity and mortality vary by patient age and comorbidities and are also affected by the experience in volume of the surgeon and medical center. Rates of 90-day mortality in the CR population were as high as 15 percent in older patients. As a result, many patients do not undergo radical cystectomy, whether it be due to surgical ineligibility or personal choice.

Valrubicin is approved for BCG refractory, non-muscle invasive bladder cancer, however, due to the modest response rates and the high risk of progression in non-responders, it is not

recommended in professional guidelines. In the study of valrubicin, 90 patients with BCG refractory CIS were treated, with 10 patients achieving complete responses at 6 months.

The median duration of response was 13.5 months if measured to time of last bladder biopsy without tumor and 21 months if measured to time of documented recurrence. Data for other intravesical therapies such as docetaxel, mitomycin C, and gemcitabine are limited with small cohorts, heterogeneous populations, and variable follow-up procedures, rendering interpretation of results difficult.

FDA has facilitated a number of discussions on study design, acceptable endpoints, and what constitutes clinically significant results in non-muscle invasive bladder cancer trials. At the FDA co-sponsored workshop in 2013, there was broad consensus by the panel that provided the results were robust. A single-arm trial could provide sufficient evidence of benefit.

For patients with BCG refractory CIS, the

panel felt that an initial complete response rate of 40 to 50 percent at 6 months and a durable response rate of at least 30 percent for 18 to 24 months, with the lower bound of the 95 percent confidence interval excluding 20 percent, could be clinically meaningful.

The International Bladder Cancer Group has also published its recommendations in 2016 regarding drug development in non-muscle invasive bladder cancer, and stated that "For patients with BCG unresponsive CIS, we recommend an initial CR rate of 50 percent at 6 months and durable response rates of 30 percent at 12 months and 25 percent at 18 months as clinically meaningful." These recommendations were based on results of studies of other salvage therapies in BCG refractory patients.

They referenced the FDA American Neurological Association public workshop and mentioned that the 30 percent durable response rate at 18 to 24 months is likely too high a criteria and may not be realistically achievable. While these prior workshops and publications discussed

potential benchmarks for what magnitude of effect may constitute a meaningful complete response rate and duration of complete response, these discussions have not occurred in the context of an advisory committee. Thus, further consideration of the risk-benefit profile of therapies in this context are needed.

The FDA developed a guidance for developing drugs and biologics for the treatment of BCG unresponsive, non-muscle invasive bladder cancer, which was finalized in February of 2018. The guidance provides a definition of BCG unresponsiveness and outlines acceptable trial design and study endpoints for non-muscle invasive bladder cancer with CIS or papillary tumors.

Key components of the guidance pertinent to today's discussion include recommendations regarding complete response as an acceptable endpoint in CIS-containing BCG unresponsive, non-muscle invasive bladder cancer; acceptability of single-arm trials in this population of patients; and parameters for the evaluation of

response rate; and the importance of durable responses to support clinical meaningfulness and complete response rates.

Although significant attention is paid to the point estimate of the complete response rate, the guidance states, "Clinically unimportant complete response rates should be excluded from the 95 percent confidence interval." In addition, random biopsies at prespecified time points are recommended to ensure accuracy of documents of complete responses but are not required.

The applicant has previously described the study design of KEYNOTE-057. The FDA considers Cohort A, comprised of patients with CIS, with or without papillary disease, to constitute the primary efficacy population for today's discussion. The FDA agrees that the design of Cohort A, including the patient population, staging, disease assessment schedule, and definition of complete response was consistent with recommendations provided in the FDA guidance to industry on BCG unresponsive, non-muscle invasive bladder cancer,

and is adequate to evaluate the efficacy of pembrolizumab in this setting.

We note that directed biopsies were prompted by abnormal findings on cystoscopy or random biopsies prompted by abnormal cytology. There were not prespecified random biopsies as specific time points on study, which was considered optional but not recommended in the FDA guidance. The rationale for inclusion of random biopsies is that approximately 15 percent of patients with negative visualization on cystoscopy and negative cytology may have CIS present if evaluated by random biopsy, however, this is not generally considered standard of care.

The discussion of the efficacy of KEYNOTE-057 is centered on Cohort A, as this is the intended population described in the proposed indication provided by the sponsor. The primary efficacy endpoint for Cohort A was complete response rate of high-risk, non-muscle invasive bladder cancer, which included CIS with or without high-grade Ta and T1 disease.

Patients were discontinued from study treatment if persistent or recurrent disease was detected at any assessment and continued with survival follow-up. The complete response rate was a point estimate calculated with confidence intervals. The key secondary endpoints for Cohort A included complete response rate of any disease, which included low-grade Ta tumors in addition to CIS high-grade Ta and T1 tumors.

The other key secondary endpoint was duration of response of high-risk and any non-muscle invasive bladder cancer. The FDA considered duration of response, excluding low-grade disease, to be more clinically relevant, as recurrence of low-grade disease does not necessarily portend a worse clinical outcome.

For the purposes of the FDA evaluation, efficacy is based on the 96 patients in Cohort A that met the FDA definition of BCG unresponsive, non-muscle invasive bladder cancer. Five patients of the 102 enrolled in Cohort A did not have adequate documentation to confirm that they met the

FDA definition of BCG unresponsive, non-muscle invasive bladder cancer. As previously noted, one patient was determined by the applicant to have been misclassified as having CIS after the briefing document was distributed. This patient has been removed from the primary efficacy results in all FDA slides.

The majority of patients were BCG unresponsive due to recurrent non-muscle invasive bladder cancer. Of note, persistent high-risk in non-muscle invasive bladder cancer is generally considered a subgroup at higher risk for progression to muscle-invasive disease than those with recurrent.

We agree with the sponsor's description of the patient's baseline disease characteristics. We note that this is an older population with a median age of 73, which is similar to that seen at diagnoses of bladder cancer in the SEER registry. Patients had received a median of 12 prior installations of BCG. The majority of patients elected not to have cystectomy as treatment for

their BCG unresponsive, non-muscle invasive bladder cancer. There were only 3 percent of patients that were documented as medically ineligible to have cystectomy due to heart disease and/or performance status.

The majority of patients had CIS alone at study entry with a minority having CIS with T1 tumors. Although all high-risk and non-muscle invasive bladder cancer is at risk for progression to muscle invasive bladder cancer, CIS with T1 tumors may represent a subgroup at particularly high risk for progression.

Patients received a median of 7 doses of pembrolizumab with a range of 1 to 35 doses. Based on FDA calculation, the complete response rate in the 96 BCG unresponsive patients with CIS was 41 percent at 3 months. The complete response rate was similar between the 96 patients who met FDA criteria for BCG unresponsiveness and the 5 patients that did not have confirmation of BCG unresponsiveness.

There was a minimum follow-up of 14 months

from the time of last patient enrollment to the data cutoff, and a median duration of follow-up of 24 months. The median duration of response, whether including or excluding recurrence of low-grade disease, was 16.2 months with approximately half of patients with complete response having their responses persist for at least 1 year.

In addition, there were 4 patients with complete response beyond 2 years. This corresponds to 19 percent of all treated patients achieving a complete response lasting at least one year. Although evaluation of complete response rate across subgroups is considered exploratory, there was no clear indication of any outlying subgroups, including the high-risk category of patients with CIS and T1 disease.

Almost all patients who enrolled on the trial had refused cystectomy and were not considered medically ineligible. Among the 79 patients, or 81 percent, who either never achieved a complete response or responded but later

recurred, 36 patients underwent subsequent cystectomy. This included 41 percent of patients with recurrent disease and 46 percent of patients with persistent disease.

Three patients, all of whom had persistent disease, were noted to have muscle-invasive disease on pathologic examination of their cystectomy specimen. With the caveat that this is a non-random sample, this rate of upstaging as cystectomy is generally consistent with that seen in other trials of high-risk, non-muscle invasive bladder cancer.

In summary, complete response rates seen in BCG unresponsive, non-muscle invasive bladder cancer with CIS, as a result of treatment with pembrolizumab, were substantially increased compared to historical controls of other available intravesical therapy. Nineteen percent of all patients maintain a complete response of a year or longer, a duration that FDA considers to be clinically meaningful.

Previous publications have reported that CIS

is detected in approximately 15 percent of patients with non-muscle invasive bladder cancer in which random biopsies were performed in the setting of negative cytology. Although not required by the FDA guidance to industry on BCG unresponsive non-muscle invasive bladder cancer, random biopsies are suggested to fully evaluate for persistent or recurrent CIS, however, they were not performed on KEYNOTE-057. This raises potential concern that a small proportion of persistent or recurrent disease could have been missed.

The primary safety population for KEYNOTE-057 consisted of the full population enrolled to Cohort A. Evaluation of safety included collection of adverse events data; laboratory assessment; patient narratives for deaths; serious adverse events; discontinuations due to adverse events; and adverse events of special interest; in addition to an audit of case report forms.

FDA agrees with the applicant's description of incidences of adverse events and immune-related adverse events in Cohort A, including a 3 percent

incidence of high-grade, immune-related adverse events. No new safety signals were identified in KEYNOTE-057, and pembrolizumab appeared to be well tolerated in a study population with a relatively low rate of discontinuation due to adverse events.

There were 2 deaths on study that the FDA did not consider related to pembrolizumab. However, deaths due to pembrolizumab related toxicity have been observed in other studies. There were no events of progression to muscle invasion or metastatic urothelial carcinoma on study in Cohort A, with the minimum duration of follow-up of 14 months and median of 24 months.

Given the natural history of high-risk, non-muscle invasive bladder cancer, and particularly BCG unresponsive non-muscle invasive bladder cancer in which the majority of progression events are likely to occur within 48 months, this duration of follow-up is reassuring but may not fully capture the risk of progression in patients treated with pembrolizumab. As noted previously, approximately 8 percent of patients who underwent

subsequent cystectomy did have muscle invasion on their pathology specimen, which is in line with expected rates of pathologic upstaging.

In summary, with the caveats of limited duration of follow-up as noted, treatment with systemic therapy and delay of cystectomy did not appear to be a detriment to patients in regards to the oncologic outcomes of progression to muscle-invasive bladder cancer or metastatic urothelial cancer.

In conclusion, the applicant is seeking an indication for the use of pembrolizumab for the treatment of patients with BCG unresponsive, high-risk, non-muscle invasive bladder cancer with CIS who are ineligible for or have elected not to undergo cystectomy. We agree that the standard of care for patients with BCG unresponsive disease is radical cystectomy, which is a morbid procedure in the generally elderly and frail population of patients with bladder cancer, and there are limited alternative nonsurgical options.

We agree that the observed rate of complete

response is substantially greater than that seen in historical controls, including valrubicin. As of the data cutoff, 19 percent of all treated patients experienced the complete response of one year or longer from the time of initial response, which may be clinically meaningful. The median duration of response was over 16 months with a small proportion of responding patients still in response beyond 2 years.

Limitations to interpretation of durability are that there were no random biopsies, which may detect occult disease missed by cytology and visual inspection of the bladder, and that despite the duration of response being reached, the long-term durability remains unclear, as few patients were followed beyond 18 months from response.

While a systemic therapy, pembrolizumab appeared to be reasonably safe in this trial. There did not appear to be a missed opportunity for radical cystectomy, as there were no progression events to muscle invasion or metastatic disease in Cohort A, with a minimum of 14 months of follow-up

from last patient enrolled to data cutoff; although this may not be sufficiently long to fully characterize the risks of pembrolizumab or the risk of progression after pembrolizumab.

Our voting question for the advisory committee is the following: Do the observed complete response rate and duration represent a favorable risk-benefit profile in patients with BCG unresponsive, high-risk, non-muscle invasive bladder cancer with pembrolizumab, a systemic therapy? Thank you for your attention.

Clarifying Questions to Presenters

DR. HOFFMAN: Thank you. We will now take clarifying questions for the presenters. Please remember to state your name for the record before you speak, and if you can, please direct your questions to a specific presenter. If you have a follow-up question pretty much on the same theme, as the last, you might put your name card upright as the signal to us about that. Thank you.

As a non-urologist, I wonder if this question has come up. With CIS, is CIS very often

a flat lesion, and therefore is it difficult to detect visually to know what should be biopsied on a cystoscopy? We've heard about the lack of random biopsies, so how difficult is it to detect CIS visually? That could be for Dr. Steinberg or one of the urologists.

DR. EBBINGHAUS: Sure. I'll have Dr. Steinberg come to the podium. While he's coming up, just to reiterate, all patients had biopsy-proven CIS at study entry.

DR. STEINBERG: Thank you. Gary Steinberg. I think that carcinoma in situ can be difficult to detect, but in my experience, in patients that have had a negative cystoscopy and a negative cytology -- and again, these are patients that have been followed, so they come in. They've had a diagnosis. They've had a treatment. They're getting cystoscopy and cytology every 3 months.

In patients that have had serial negative cystoscopies and cytologies, in my experience, if I do random biopsies on those patients, it's akin to finding a needle in a haystack. I think that in my

own personal experience of 30 years, the rate of finding carcinoma in situ in this scenario is exceedingly low, and I think it would be much less than a few percentages.

DR. HOFFMAN: Dr. Cristofanilli?

DR. CRISTOFANILLI: Great data. One question, obviously, that comes from a medical oncologist who doesn't practice urology, the PD-L1 expression doesn't have to be any predictive value in this in situ disease if there is any correlation to duration of response in the patient that achieves complete response. Have you tried to identify PD-L1 positive in the cytology on the cells that were collected, the cytology?

DR. EBBINGHAUS: The PD-L1 expression level has been an important biomarker for the development of anti-PD-1 therapies. With pembrolizumab, we had the first companion diagnostic, so we've evaluated PD-L1 expression across all of our trials. What we found is while there tends to be a correlation between outcomes and PD-L1 expression, the clinical utility of PD-L1 expression varies by the disease

context, meaning the tumor type, the stage of disease, and whether pembrolizumab is used alone or combined with another agent.

In this case, we found no real good correlation between the level of PD-L1 expression and the initial response rate. To answer your question, we didn't find that there was any correlation or a difference between the durability of response in patients who were PD-L1 high or PD-L1 low using the cutoff point of 10. We have not yet evaluated or attempted to find PD-L1 expression in urine cytology specimens. That's an interesting thought.

DR. HOFFMAN: Dr. Pavlovich?

DR. PAVLOVICH: I just have two questions. Maybe Dr. Steinberg would be reasonable to field. One is, in following up with your question about cytology and CIS, and how it's difficult to see, there is a technology. There are several technologies to make these lesions more visible, and Dr. Steinberg and others have worked with those. One is called blue light cystoscopy and the

other is called narrow-band imaging. Collaborative groups have shown that one can find lesions that might have been missed, say, in about 20 percent of patients. You'll only see something with this new visual technology.

So my question is, was that considered? Was that used in some patients in this trial, and if not, why not?

DR. STEINBERG: So excellent question. There was consistency so that if a patient was diagnosed with white light, they were followed with white light. If they were diagnosed with Cysview and blue light, they were followed with that. The issue is that, currently, 188 centers in the United States have around 2500 centers that perform cystoscopy and biopsies that have Cysview and blue light available. That's also true in various parts of the western world and eastern world.

Because of that, the standard of care today continues to be cystoscopy with white light. It's just not feasible to perform these types of trials in this patient population solely at centers with

blue light; and more importantly, you then would not be able to translate your results to the standard of care throughout the U.S. and the world.

DR. PAVLOVICH: My other question is I just want a clarification, perhaps from you or from the sponsor, that the CR that we are looking at of about 41 percent was a -- am I correct -- 3-month cystoscopy and cytology?

DR. STEINBERG: Correct.

DR. PAVLOVICH: Thank you.

DR. HOFFMAN: Dr. Klepin?

DR. KLEPIN: Thanks. Heidi Klepin. I have two questions, both for the sponsor. The first is about a little more granular characterization of the patient population. This was appropriately an older adult patient population. My question relates to whether or not you have any comorbidity data so that we could better understand these older adults as we think about generalizability.

DR. EBBINGHAUS: Dr. Kapadia, would you want to answer that question about comorbidities?

DR. KAPADIA: Given that the median age was

73 on KEYNOTE-057 and approximately 45 percent of patients were 75 and older, a majority of patients did have quite significant comorbidities coming on to this study, which included cardiac as well as renal disorders, as well as other -- like diabetes, et cetera. We don't have an exact table listing out all the comorbidities, but a majority of patients did have comorbidities that you would expect in an elderly population.

DR. KLEPIN: May I just ask a second question? The second question relates to the safety trade off. Do you have any information around the complication rate post-cystectomy for those patients who did go on to get cystectomy?

DR. EBBINGHAUS: We didn't directly collect postoperative complications in the patients who had a cystectomy on this trial. That wasn't collected as part of the study procedures. None of those patients have had mortality, and perioperative mortality can be quite high in patients with a cystectomy.

We have several trials evaluating

pembrolizumab in the setting of muscle-invasive bladder cancer, so those will be settings where patients get preoperative pembrolizumab and then undergo a cystectomy. One of those we've seen data from. There don't appear to be any increased risk of giving pembrolizumab preoperatively in the neoadjuvant setting prior to a cystectomy. And we have an extensive neoadjuvant program in multiple tumor types, so we don't see any trends for increasing perioperative risks with pembrolizumab.

DR. HOFFMAN: Dr. Halabi?

DR. HALABI: Thank you. I have a couple of questions for the sponsor. I'm curious. If you'd refer to CE-14, slide CE-14 -- and again, I know this is a subgroup, but it seems in some of those subgroups, such as CIS with high-grade Ta and others like U.S. region, you can look at the lower bound, and it was below 20 percent. So I'm curious to hear your thoughts on why is that. Also, I would like to know whether a CPS greater than or equal to 10, if that was prespecified in your protocol and the cutoff point.

DR. EBBINGHAUS: The answer to your first question is we interpret this forest plot to generally show that there are no consistent trends for greater or lesser responding subsets across the population of patients that were tested in this protocol. Of course, given that it's a 96 patient total population and some of the subgroups that you've mentioned have 20 or 30 patients, some degree of variability would be expected. We interpret these data to generally show a high degree of consistency across subgroups; no real outliers.

The second question was about the cutoff point for PD-L1 expression. The level of PD-L1 expression or the PD-L1 expression score of CPS-10 was prespecified for this protocol. It was informed by an evaluation of a prior study in your urologic disease or in urothelial cancer based on KEYNOTE-052.

DR. HALABI: Thank you. A follow-up question. Do you have data on time to cystectomy or the median time to cystectomy among those

patients who already had cystectomy?

DR. EBBINGHAUS: The median -- I'm sorry. Let me make sure I understand the question. The question is do we have data on the median time to cystectomy in those who had a cystectomy?

DR. HALABI: Among those who had cystectomy, what is the median time from initial treatment?

DR. EBBINGHAUS: I do have some data that can inform on that, and I will just pull it up here. I don't have data that directly answers from the start of treatment, but the interval from the last dose to the cystectomy is shown on this table for the patients that had a cystectomy. It's around 3 months for most of the patients.

DR. SUZMAN: We did conduct that analysis. Bearing in mind that this was essentially -- I believe it's backup slide 31, the FDA slides. Bearing in mind that this was essentially a responder analysis and, as such, was non-random and possibly biased, and additionally given that cystectomy generally occurs soon after loss of response, these outcomes were largely captured by

the median duration of response.

Nevertheless, the difference in time to cystectomy between those who were never responders and those who had a complete response with subsequent occurrence is shown here. The differences is about 5 months.

DR. EBBINGHAUS: I think it's important to also -- while that was an interesting responder analysis, it's also important to note that the patients who had responses that were durable were not included in that. In other words, those patients who remained in response are not included in that analysis.

DR. HOFFMAN: Dr. Kraus?

DR. KRAUS: It's really a follow-up question to the response rate and the determination of CR at 3 months, I guess. If I remember the design, but correct me if I'm wrong, it looked like patients were mandatorily discontinued from therapy at 3 months if indeed they weren't responders.

So I'm just wondering if you have information on time to response because it might be

there would be additional responses if therapy continued. I know, given the mechanisms of immunotherapy, et cetera, in some settings, perhaps there'd be additional responses that wouldn't be captured in the 41.

DR. EBBINGHAUS: In this case, the first evaluation was at 3 months, and since patients were required to go off therapy after 3 months, we really don't have data that could inform on that possibility, but it is an intriguing thought. In other disease states, about two-thirds of responses are recorded within the first 3 months, and there are quite a number of patients who have responses that are delayed beyond that. But in this particular case, the responses were generally recorded at month 3, give or take a few weeks, depending on how procedures could be scheduled.

DR. HOFFMAN: Dr. Agarwal?

DR. AGARWAL: I have a question on cytology. I know that the pathology was centralized, but was cytology reviewed centrally? The second question on cytology is often places have positive or

negative, and then some sort of in between, atypical, or reactive, or something that's in between. How was that handled in the course of the trial?

DR. EBBINGHAUS: The answer to your first question is quite simple. Yes, we did review the urine cytology centrally at the same central vendor that reviewed the pathology specimens, and there was an intermediate category between negative and high grade, which was called "suspicious." Those were handled -- correct me if I'm wrong. Those were not handled as if they were considered positive, in terms of the definition of -- in terms of -- wait, is that correct? Sorry.

Why don't you come up here and just explain? Sorry.

DR. KAPADIA: So as Dr. Ebbinghaus mentioned, for urine cytology, all urine cytologies were reviewed by a central vendor, and we had a negative category, atypical, suspicious, and positive for high-grade UC. So patients who were atypical were considered negative. Patients who

had suspicious were required to undergo random biopsies of the bladder, as well as prosthetic urethra in males for further evaluation.

DR. HOFFMAN: Dr. Siddiqui?

DR. SIDDIQUI: I have two questions. One is, I know it's a small group, but in the patients that progressed to cystectomy, do you know what the breakdown was of the T2 and higher disease between the complete responders who ultimately progressed versus people who just got cystectomy right away because they never responded?

DR. EBBINGHAUS: I'm sorry, I don't -- there were only 3 patients that progressed to muscle-invasive disease. Of those, 2 patients had T2 and one patient had T3.

Can you clarify your question?

DR. SIDDIQUI: Were those 3 patients, patients that had gone directly to cystectomy after not responding versus first responding, and then ultimately --

DR. EBBINGHAUS: Yes. None of those 3 patients had achieved an initial complete

response, so they were never in response. The time to cystectomy varied from 60 days to about one and a half years. So 1 of the 3 patients that recurred waited about a year and a half to have a cystectomy.

DR. SIDDIQUI: And the second question was there have been some comments about no random biopsies in your protocol. Did no one get a random biopsy or was there some proportion of the population that did and did not get random biopsies?

DR. EBBINGHAUS: Random biopsies were required only for patients that had a suspicious or higher cytology, so I don't believe we collected data on whether patients had random biopsies that weren't for that cause.

DR. HOFFMAN: I have a question for probably Dr. Kapadia on slide CE-12. My apologies if I missed the boat somewhere. On the disposition, we have 96 patients to start and 3 completed 2 years of pembrolizumab. But yet we have data about the duration of responses and so on, and the protocol

specified up to 2 years of pembrolizumab if they are still in response. I believe that's correct.

Could you explain it? I feel like we missed a bunch of people here.

DR. KAPADIA: So 96 patients were part of the efficacy population, and the majority of patients, approximately 60 percent, came off at the first efficacy assessment around week 12 because of the reasons you see on the right side. The most common reasons were persistent NMIBC or recurrent NMIBC.

DR. HOFFMAN: Well, 86 people then, of 71 had persistent or -- is that right?

DR. KAPADIA: Right.

DR. HOFFMAN: Okay.

DR. KAPADIA: So 3 patients had completed a full 2 years of treatment with pembrolizumab, and then there were 3 additional patients who had electively discontinued after 18 months. This was allowed in the protocol in patients who continued to have an ongoing response. They could discontinue after 18 months. On the right side in

teal, you can see that there were 3 additional patients, then at the time of data cutoff, there were 7 patients who were still receiving treatment.

DR. HOFFMAN: So did I hear you correctly earlier that the average number of doses or infusions was 7?

DR. KAPADIA: Yes. I believe the FDA presentation --

DR. HOFFMAN: Oh, I'm sorry.

DR. KAPADIA: -- quoted that number, yes.

DR. HOFFMAN: Okay. Thank you.

Dr. Apolo?

DR. APOLO: I have some questions about the adverse events. There were some serious adverse events that were reported, including respiratory failure with an MRC; pneumonia that was unrelated; hyponatremia and nephritis; type 1 diabetes; and hepatitis. Were these adverse events associated with the responders, the 19 percent that were responding at one year, or do you have this data? Maybe the FDA has this data.

DR. EBBINGHAUS: We have evaluated the

safety of pembrolizumab. I think the question, you can sort of broaden it a little bit to say the time of onset of adverse events. We've looked at the timing of onset of adverse events across our program. The data on that is well described in our product labeling, based on a reference safety data set. What we saw here was generally consistent with what we've seen across the program with respect to the timing of onset of adverse events.

So the immune-related adverse events, or the adverse events, were seen in patients, both in the responder population, as well as the non-responder population. But those adverse events, particularly the immune-mediated ones that were clinically significant, that were relatively low in number, were generally manageable and resolved.

DR. APOLO: But I guess my question was, were the responders the ones that had the adverse events or it was just distributed throughout? I don't know if that data's available.

DR. EBBINGHAUS: I'll as Dr. Wivel from product safety to come to the microphone.

DR. WIVEL: Ashley Wivel from Merck drug safety. We actually have not conducted an analysis of the adverse events by responder status. We are aware that there is some literature out there looking at whether people who have immune-mediated adverse events actually may have a difference in efficacy, but so far, those have been really hypothesis generating. What I can say, as Dr. Ebbinghaus said, is that we've seen a very consistent safety profile across all the people studied in KEYNOTE-057, but I don't have data to show you for the individual response status.

DR. BREWER: The FDA also did not conduct a specific analysis to determine if adverse events were more frequent in responders versus non-responders.

DR. HOFFMAN: Dr. Hinrichs?

DR. HINRICHS: I just wanted to clarify around the primary endpoint. The primary endpoint was the CR rate. In designing the protocol, did you prospectively set a bar for what would determine a positive outcome versus a negative

outcome for the trial in terms of what that response rate needed to be?

DR. EBBINGHAUS: Yes, we did. We set a bar that was intended to exclude an uninteresting complete response rate. I'll just show this slide again. So we prespecified that the lower bound of the 95 percent confidence interval should exceed 20 percent, which it did in this trial.

DR. HOFFMAN: Are there any other -- Dr. Agarwal?

DR. AGARWAL: Do we know the breakdown of how many patients had blue light cystectomies and how many had white light? I know it was uniform for when they had it, but I just want to know what percentage had their evaluations under blue light and what had it under white light.

DR. EBBINGHAUS: I think underscoring the fact that the blue light is not widely available, only 6 of 96 patients had consistently used blue light cystoscopy throughout the trial.

DR. HOFFMAN: Dr. Hawkins?

DR. HAWKINS: Correct me if I'm wrong, but I think that some initial data was the International Bladder Group made recommendations of complete response, 50 percent at 6 months, 30 percent at 12 months, 25 percent at 18 months. How well did we do in the study compared to those recommendations?

DR. EBBINGHAUS: I think the guidelines that you've seen set a really important framework, and some of the people here were actually integral to those discussions and those guidelines. I'd actually like to ask Dr. Ashish Kamat to come up and discuss the results of KEYNOTE-057 in context of the guidelines.

DR. KAMAT: If I may just give a little background, and kudos to the FDA back in 2013 for reaching out to the AUA and coming together for the workshop. As you saw in that workshop, there was a discussion of a bar as to what we should try to achieve in this patient population, simply because all the trials before that point had looked at any patient that had a recurrence after BCG therapy, and it was not a uniform definition.

So we were trying to come up with uniform definition, and looking at the older literature, which was in a very heterogeneous sometimes lower risk patient population, sometimes higher risk patient population, the discussion of the bar had been set fairly high, at 30 percent at 18 to 24 months, which, again, Dr. Wivel mentioned when she was discussing it, that that was considered by many to be not really attainable.

So the International Bladder Cancer Group, which I lead, when we came together, again, sort of at the informal behest of the FDA, to look at that bar and come up with other numbers, we were still not in this high-risk BCG unresponsive population. But we felt that 30 percent at 18 to 24 months is way too high, so we adjusted that to about 50 percent at 6 months, and then it should be durable to about 25 percent at a year or two, a year and a half.

But again, that was keeping in mind that it may not be a very strict definition of patients as far as entry criteria is concerned. KEYNOTE-057 is

a very strict BCG unresponsive, so the highest risk category is within the patients who have recurrence after BCG. We don't really have historic controls for this population, and clinically, just having taken care of many patients with this disease, it is a clinically meaningful response rate, again, comparing with a lot of the other agents out there.

DR. HOFFMAN: Dr. Pavlovich?

DR. PAVLOVICH: For Dr. Kapadia, following up on the side effect profile, because I think the safety is going to be a big factor in our decision making today, the immune-mediated adverse events on slide CE-25 list a lot of one-patient events, as well as hyper and hypothyroidism and pneumonitis.

I guess my question is -- this is a systemic therapy for what may not yet be a systemic disease -- how many of these side effects are longstanding, permanent? Did these just go away with this continuation or are we having to supplant adrenal steroids forever, or thyroid hormones forever, or does someone have uveitis for years and years? Just a little more granularity on that,

please.

DR. EBBINGHAUS: In general, the adverse events in KEYNOTE-057 were quite similar to the adverse events that we've seen across the program and, in general, the adverse events resolved. The one exception to that is with the endocrine disorders. Endocrine disorders are often long-lasting. We've only had data going for 5 or 6 years, so we can't use the word "permanent" but they can be long-lasting and they may require endocrine supplementation.

So in the 8 percent or so of patients who had hypothyroidism, they may require Synthroid or thyroid supplements longer term. The remaining adverse events that aren't endocrine related generally resolve.

DR. HOFFMAN: Dr. Klepin?

DR. KLEPIN: Heidi Klepin. Sorry to make you redundant on this, but this is actually going back to Dr. Hawkins' question about the recommendations from the International Bladder Cancer Group, and I just wanted to be a hundred

percent clear. So the recommendation for a durable response rate of 30 percent at 12 months would correspond to the 19 percent that we're seeing. So that's based on the total population? So those two numbers would be the ones we would sort of compare to one another?

DR. EBBINGHAUS: I think those numbers are pretty hard to compare. Duration of response, by definition, should be measured in a responding population, but we translated that number. So about half of our responses are durable out to a one-year landmark, and we've translated that number into about 20 percent of the total population, who ever received a dose of pembrolizumab, but remembering that many patients are going off study after only 3 months. This is a meaningful response, and many patients have even longer responses.

The only other point is because we're measuring complete response in the responding population, you start the clock from when response is first recorded, not from when treatment has

started. In comparison to some literature, in the urology literature, they often measure complete response rate from the initiation of therapy, so you'd have to sort of mentally adjust this by adding about 3 months to the durability of response data.

DR. HOFFMAN: Dr. Apolo?

DR. APOLO: Thank you. Non-muscle invasive disease is usually seen and managed by the urologist, but the systemic therapies are generally given by the medical oncologist. I know some of these patients were not treated in the United States.

What was the requirement for treatment of these patients? Was the pembrolizumab given by the medical oncologist, and is that something that, if approved, it would be recommended that the treatment continue to be given by the medical oncologist; or if it's approved, it could be given by the urologist as well?

DR. EBBINGHAUS: About half of the sites that were involved in KEYNOTE-057, the

pembrolizumab was given by urologists. We have an extensive plan of helping to be able to allow this treatment to be given in urology practices, and perhaps Dr. Kamat or Dr. Steinberg could come to the podium and discuss their perspective on giving pembrolizumab in a urology office. It's not intended that we would limit this to only being administered by medical oncologists.

DR. KAMAT: Again, at our center, we work very closely with our medical oncologists, and our medical oncologists administer the drug. But, in general, in the urology community, both in the U.S. and internationally, there's been a lot of interest -- because we see these non-muscle invasive patients for years and years and years, and urologists have good rapport with them, there's an interest in learning more about the administration of systemic IO agents.

For example, the AUA, American Urological Association, the European Association, SIU, which is the international society, they have workshops and educational symposia, educating urologists, and

those that are in centers where they may not have access to medical oncologists, on how to administer and also deal with the adverse events when it comes to systemic IO agents.

There are some countries in the world where it's routinely administered by urologists, but in countries where it's not, there's an ongoing effort by our larger bodies to educate the urologists on how to take care of this. But at our center, and in most academic centers, I suspect, it will still be a partnership between the urologists and the medical oncologists.

DR. HOFFMAN: Dr. Murdock?

DR. MURDOCK: Is there a theory as to why the PD-L1 status of the patient does not affect the response to the treatment?

DR. EBBINGHAUS: As I've mentioned, in general terms, PD-L1 expression has correlated well with outcomes or particularly response, however, the context of the disease has been quite important. In different tumor types, the degree of predictive value of PD-L1 expression has varied.

In KEYNOTE-057, we didn't see that there was a correlation between PD-L1 expression status and response to therapy; a few potential reasons why that could happen, but in this case, there's no easy explanation to explain why high or low PD-L1 expression didn't correlate; just to say that the utility of PD-L1 expression has varied by disease type, as well as the disease context or the stage of disease.

DR. HOFFMAN: I had a question about the cystectomies, recognizing that the purpose of this approval, or the purpose of using this drug, is to delay or prevent the need for cystectomy. So again, I'm looking at the disposition; 36 patients, if I'm correct, had a cystectomy. Some of them who did not are still on treatment or still in response. They may be off the drug, but are still fine. That's the entire -- the other 60 some are in response, not progressing, or they still chose not to have cystectomy, and may have gone on to metastatic disease and so on.

DR. EBBINGHAUS: Time to cystectomy has not

generally been able to be used as an endpoint in a population like this because the use of a cystectomy depends on a lot of factors. This was a population of patients who initially declined to have a cystectomy in about 95 percent. So the disposition of patients who didn't have a cystectomy, many of those patients went on to have other nonsurgical therapies such as TURBTs or other intravesical treatments. About 10 percent had no therapies at all, and about half of the patients that never achieved a CR eventually went on to have a cystectomy.

I think this just underscores that this is a population of patients who are really desperate to avoid having a cystectomy, and even after going off of pembrolizumab, in many cases won't go on to have a cystectomy, and here are the numbers.

Let's try that one more time. Anyway, the number of patients who had no subsequent therapy was about 10 percent of the total population. I have a glitch on getting the slide up.

Did I address your question, Dr. Hoffman?

(Dr. Hoffman gestures yes.)

DR. HOFFMAN: Dr. Apolo?

DR. APOLO: I want to go back to the adverse events. There were patients that had pneumonitis, colitis, nephritis. How many patients in general required immunosuppressive agents because of an adverse event, like high-dose steroids or others?

DR. EBBINGHAUS: I'd like to ask Dr. Wivel to come to the podium and help describe those data.

DR. WIVEL: Ashley Wivel, drug safety. So we have seen pretty consistently across the pembrolizumab program approximately 30 percent of participants who get immune-mediated adverse events get steroids to treat them, and that number needs to be seen in the context that the most common immune-mediated adverse events are actually hypothyroidism and hyperthyroidism, which don't require steroid therapy.

So what we saw in KEYNOTE-057 was very consistent with what we've seen in our reference safety data set, and a proportion of patients do receive high-dose treatment in accordance with our

protocols and also with our product labeling.

DR. APOLO: So about 30 percent in this trial.

DR. WIVEL: Overall received steroids. I think we're not able to bring up the slide to show the proportion that had high dose. Sorry. Thirty percent of those who had immune-mediated adverse events received steroids. Is that clear?

DR. APOLO: That's better.

DR. WIVEL: Okay. Thank you.

DR. EBBINGHAUS: Thirty percent of the 20 percent that had an immune-mediated event had a high-dose corticosteroid. But I think the important message is that this is a generally well tolerated treatment that is acceptable in this population.

DR. HOFFMAN: Any other questions from the group or clarifications?

(No response.)

DR. HOFFMAN: Okay. We'll now take a 15-minute break. We're a few minutes early. 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 why don't we plan to resume about 3:20.

(Whereupon, at 3:05 p.m., a recess was taken.)

DR. HOFFMAN: Dr. Steinberg, did you want to clarify something from an earlier -- oh, okay.

DR. KAMAT: Thank you for the opportunity. I just wanted to clarify something for Dr. Klepin and Dr. Hawkins because you did ask the question about the International Bladder Cancer Group and the numbers that we had put forward in our publication in 2016.

At the time that we gathered and discussed those numbers with the experts and the statisticians, those numbers were not meant to be hard benchmarks to compare any treatment outcome against. They were more meant to help with the statistical design and design of the clinical trials. Clearly, in this study, the important thing to remember is the responder analyses, the 41 percent response rate, and then 46 percent of

those responders had a durable response beyond 12 months; so the median duration response, 16.2 months.

So we can't really compare with the benchmarks that were put into the manuscript or the IBCG guidelines because they weren't meant to be benchmarks, per se, but more just to help with trial design parameters. I just wanted to clarify that since that was brought up a few times.

If I might, because the other question that was raised by Dr. Apolo was the risk-benefit in managing these patients with non-invasive disease and toxicity, and Dr. Balar treated a lot of these patients.

DR. BALAR: Thanks, Ashish. Arjun Balar, medical oncologist.

Andrea, you touched on a very important issue, which is that for patients treated with systemic agents, how do we manage the safety of these drugs? I think I'll first start off by saying that when we look at adverse event tables, we look at grading of toxicity, and sometimes we

just define grade 3 and 4 as being terrible, and then everything else is manageable.

I think you and I both agree that grade 2 nausea that lasts for weeks on end is a terrible toxicity for patients, and that could be relatively compared to a grade 3 that lasts for a few days. In my experience, having treated, much like you, many hundreds of patients at this point with bladder cancer, in various stages of their disease, including metastatic, muscle invasive, and non muscle invasive, the safety profile I have observed with this drug has been fairly consistent.

The immune-related adverse events, while they do occur, they do occur in a minority of patients, and with experience we intervene very, very quickly with corticosteroids, and the events generally lasts for 1 or 2 days and resolve almost completely in the majority of patients. We do see irreversible toxicity that's mostly in the form of endocrinopathies, but the majority of those cases are hypothyroidism, thankfully, which leads to a lifelong thyroid replacement. But generally,

impact on quality of life, long term from those adverse events, was actually quite minimal, in my experience.

Open Public Hearing

DR. HOFFMAN: Thank you.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, it's direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at 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 today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. I appreciate your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the

record.

MS. MADDOX-SMITH: My name is Andrea Maddox-Smith, and I'm with the Bladder Cancer Advocacy Network. Thank you for the opportunity to speak today. The Bladder Cancer Advocacy Network, or BCAN as we are called, is a patient advocacy organization. We raise awareness of the disease and provide education and support for those in the bladder cancer community.

BCAN encourages and helps to facilitate research into safe and effective new ways of diagnosing and treating the disease, as well as improving patient outcomes. We represent the more than 80,000 people who will be diagnosed with bladder cancer this year alone, as well as the countless loved ones who care for them. We also represent the more than half a million estimated bladder cancer survivors in the United States who are attempting to manage this disease, the most costly cancer to treat over a patient's lifetime. A sad reality is that 17,000 people will die from bladder cancer this year.

Bladder cancer is the sixth most commonly diagnosed cancer in the United States, yet ranks 24 in research from the National Cancer Institute. Bladder cancer is a disease with a high rate of recurrence. Some estimate its recurrence rate to be nearly 75 percent within 10 years after diagnosis.

For most patients, bladder cancer requires regular active invasive surveillance every few months. Approximately 7 out of 10 of all new diagnosis of bladder cancers are classified as non-muscle invasive. This means that the tumor has not invaded the muscle layer in the bladder. Roughly 1 in 4 initially non-invasive cancers progress to invasive types during the person's lifetime.

The majority of patients with muscle-invasive disease require surgery to remove the bladder, as well as surrounding organs, a complicating and life-altering operation. While there have been advances in the diagnosis in the treatment of bladder cancer over the last few years

for many patients with non-muscle invasive disease, the standard care involves BCG immunotherapy drug placed directly in the bladder. There has been a shortage of this drug for more than a year, leaving patients without access to potential life-saving treatments. Additional treatment options for bladder cancer are desperately needed.

So on behalf of our community, we want to emphasize the critical need for FDA to fully explore all viable options for treating and managing this disease. Thank you for your time.

DR. HOFFMAN: Thank you.

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

DR. ZUCKERMAN: I'm Dr. Diana Zuckerman. I'm president of the National Center for Health Research. Our nonprofit research center conducts and scrutinizes research that is aimed at improving treatment and prevention. We do not accept funding from pharmaceutical or device companies, so I have

no known conflicts of interest.

I'm here today -- my perspective's a little different. I started out my career as an epidemiologist. I was on the faculty at Yale and Harvard, but then I came to Washington over 30 years ago, and I've really focused on health policy issues since then.

I've been to FDA advisory committees for over 30 years. Probably not too many people here can say that, but I've really seen some changes. One of the changes that's really happened recently has been the way that information is provided to the advisory committees, including this one, based on the data from the sponsor and FDA's analysis of it. So that's what I really want to talk about a little bit today as it pertains to this product.

There have been a lot of very important questions asked by panel members, and I thought that while our center usually has someone come to speak about the data, we did not feel that we could do that today because we felt that we didn't have the kind of information we usually have in the FDA

memo regarding the data.

I don't know if you felt that way, too, whether you felt that you were lacking information, but you've asked a lot of questions that I thought were very important, things like comorbidities. We would also be wondering about data, whether there are sex differences and age differences, or racial differences. I have not served on an FDA advisory committee, but I did serve on the CMS Medicare Coverage Advisory Committee, so I have some sense of the importance of the written information, not just the information that's presented orally at the meeting.

We just wanted to say that we felt that the way the information was provided to you as advisory community committee members and to those of us in the public, because it seemed very logically presented, this is what the industry says, the sponsor says, and this is how the FDA responds to it, but it didn't really capture some of the kinds of information that has been provided in the past. So I just want to use a couple of quotes from the

written summary that we did find that seemed in some ways almost after thoughts compared to the way it was presented.

The fact that the drug appeared to be "well tolerated," quote, "in this patient population, however, it is a systemic therapy with potentially life-threatening toxicities."

Another statement towards the end, I think it was page 38 of the material, said, "Although the efficacy results of KEYNOTE-057 show a significant improvement over available nonsurgical therapies, it's not yet clear whether this improvement is sufficiently clinically meaningful to warrant approval in the setting of the toxicities of a systemic therapy."

I'm not here to recommend how you should vote. I'm here to ask you if you feel that you had the kind of information you wanted to help prepare you for this meeting prior to being here. And if not, I hope that you'll let FDA know that you do want more information.

I'm very sympathetic, obviously, to patient

groups who want more treatment. I heard and was very sympathetic to the idea that many bladder cancer patients do not want surgery, and they will, quote, "try anything." But my goal as a scientist and as a policy person is to make sure that when the FDA makes a decision, it's based on the best possible data and an analysis of all the data that are available. Thanks very much.

Questions to the Committee and Discussion

DR. HOFFMAN: Thank you.

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

Just to reiterate, the question that is before us, do the observed complete response rate and duration represent a favorable risk-benefit profile in patients with BCG unresponsive, high-risk, non-muscle invasive bladder cancer with CIS treated with pembrolizumab?

We'll now proceed with the questions to the committee, this question to the committee and panel discussions. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. If there are no questions or comments concerning the wording or the question, we'll now open the question to discussion.

DR. HOTAKI: Just a reminder, don't state how you're going to vote; just generate robust discussion around the question.

DR. HOFFMAN: I have a couple of comments, the 30-year and the 30,000 foot view here. On the one hand, we're discussing a systemic therapy for what is essentially a local problem, and it's not unheard of, but that's something new.

We have talked about the risks of immunotherapy, which generally are very mild, except when they're not. As a medical oncologist, I say to my patients -- I'm mostly a lung cancer doctor -- that anything can happen to any patient

at any time; whereas with chemotherapy, we kind of can predict who's going to have a tough time and who's not going to have a tough time.

So most of the time, it really is no big deal, and the thyroid problems are in fact, I think, permanent, but not life threatening. But some of the other things usually are resolvable, like pneumonitis and hepatitis, except not always. On the other hand, I agree with what's been said by the urologists that the risks of radical cystectomy, readmissions, complications, and ongoing problems are not to be taken lightly either because I also see those patients frequently.

In the lessons of oncology over the last 30 or 40 years, we have a modality that is useful in advanced disease, and we gradually move it forward to less advanced disease to the adjuvant setting, and now we're even earlier than the adjuvant setting, almost the preventive setting. Is this just another example of that?

I've got multiple hands, on this hand, on this hand, on this hand. I've got an octopus here,

I realize.

(Laughter.)

DR. HOFFMAN: I'm conflicted, and I will welcome some input from my colleagues on the panel. Dr. Hawkins?

DR. HAWKINS: Thank you for expressing that. I really wanted to get some input from anybody, but particularly the urologists on the panel, because in some ways I find myself thinking I'm kind of temporizing a bit, getting back to our chair's question, one of his questions earlier, because some people eventually wind up having surgery anyway, and there's a delay. Other individuals didn't have surgery and had something done to them. I'm not sure what that something was. They may have felt better or not, not having surgery for a period of time, and they may have had some symptom that they tolerated with the temporary drug.

So I'd like some feedback about that kind of stuff to help me with my decision because I'm a little bit conflicted as well.

(No response.)

DR. HAWKINS: Did anybody understand what I was saying? Sometimes I mumble.

DR. HOFFMAN: I was looking to see who wanted to -- Dr. Uldrick? You don't necessarily have to answer his question. I think it's somewhat rhetorical. Dr Pavlovich?

DR. PAVLOVICH: None of us want to take that on, but thank you.

(Laughter.)

DR. PAVLOVICH: I think in response to what you're saying and in conjunction with something that I've been thinking looking at this, there was at some point in one of these briefing books a concept that they were delaying cystectomy. In fact, many people are going on to cystectomy, or they will go onto it, because, really, if it's metastatic, then they're going on to systemic chemotherapy. But everybody else in the end, unless we truly have some durable responders beyond the length of this trial, which would be 40 percent of the 40 percent minus a few more, and now you're getting down to single digits, they're all going to

get their bladders out.

If you delay that, they're only getting older and less healthy, and at higher risk of T3 disease, and at higher risk of a cystectomy that is not going to be curative. So there is, in some sense, in our field and certainly in my mind -- and these guys are actually more bladder cancer experts. But there is a danger to just pushing off the cystectomy with a therapy that is not effective, let alone has some risks.

So if the therapy is effective, and it can delay it a long time, or reduce the burden of disease, or get you cleaner margins, then there's some sense, but there's also a danger, that I don't think has been really addressed, in just kind of pushing it off, and we're looking at 3-month CRs here. And maybe in stage 4 disease advanced lung cancer, that's a homerun drug that gives you three more months of life. Three months here is pretty much meaningless.

DR. HOFFMAN: Dr. Siddiqui?

DR. SIDDIQUI: Jumping in on this same

topic, I think that's a very meaningful question that was asked, or thought that was posed, about confusion about what happens to these patients, because I think that it reflects the field right now that affects urologists in general. I think one thing that you can see is actually -- one of the tables, it goes through what happened to these patients after they were treated, and you'll notice there's -- how many, 1, 2, 3, 4, 5, 6, 7, 8 -- 9 different types of intravesical therapies ever given to this mixed population after they failed to respond.

I think that is a good capture of what's going on right now out there, is that patients come in, and if BCG doesn't work, you're kind of at a loss as a urologist as what to do. So people are kind of favoring trying gemcitabine; mixed data on how useful that is intravesically. Logistically it's a little bit challenging because it's something we're not used to doing in our clinics, so we're working with oncologists, but oncologists are not clear what to do with intravesical therapy,

so that's a mess.

To me, though, what Dr. Pavlovich was saying is actually exactly also the way I think about it, that this patient population, if we're giving them a drug and a decent number of them are going to progress, are they worse off having gotten this drug now? How many people are becoming non-candidates for surgery who would have been candidates for surgery? Because surgery is a fairly curative procedure in this population.

Based on that same table, I think I'm a little bit reassured on that point because it looks like the people who were initial complete responders but then progressed, 43 percent of them got cystectomy versus 46 percent of the never responders. That confusion of what's going on with this patient population really reflects what urologists are dealing with and the lack of kind of guidance that urologists have in general as to how to manage this disease because no one's using valrubicin, really, so then it's free for all.

DR. HOFFMAN: Dr. Agarwal, you had a

comment?

DR. AGARWAL: Yes. Just to echo what my colleagues have said here, I'm really conflicted. I desperately want a therapy for bladder cancer patients, but if that therapy is ultimately resulting in half the patients getting a cystectomy 16 months, 13 months down the road, and in the context of a trial where we didn't do random biopsies and we didn't use blue light, which is known to really pick up cases of CIS, are we really looking at a 46 percent, 3-month complete response or is it much lower than that?

So again, I desperately want something because it is the wild west in terms of what to put in someone's bladder, and there's no established guidelines after BCG fails to help the patient. But I have concerns about using a drug, based on the data that was presented here today.

I have personally treated patients with IO agents, and I have seen rarer toxicities, but they do happen. The side effect profile in this group of patients is more favorable than what I've

personally seen, and I think that I'm conflicted. I desperately want to find new agents, but I think we have to also put this data in context of are we really benefiting the patient because they're just going to be older, less healthy, and now potentially -- I mean, there were at least 3 patients -- I know the upgrading rates weren't that high, but there were 3 patients who had upstaging to T2 and some had neural disease, and for those patients, the therapy did not benefit them.

DR. HOFFMAN: Dr. Uldrick?

DR. ULDRICK: Thank you. I wanted to commend the sponsor on what I thought was a really nicely conducted study. There were some elements that I thought were particularly good. The population study was clinically well defined, but I think more importantly, the endpoints for what would be considered clinically meaningful were based on consensus from regulatory agencies and professional societies.

The CR at 3 months and the durability of response seemed to be endpoints that the community,

in general, approved of, and the study seemed to demonstrate, for the 3-month CR and arguably for the duration of response, that pembrolizumab does meet those criteria.

With the limitations of monitoring the disease using blended biopsies or more modern techniques for looking at the bladder, I do think that they met the criteria that they set out for themselves. I also was pretty convinced of the need for alternatives for cystectomy, and really don't think I was aware of how morbid both short-term and long-term morbidity is for this patient population with cystectomy, in terms of the long-term side effects, metabolic, quality of life, and otherwise.

So when I look at the risk-benefit, I do see that the adverse event profile of an IO agent that's managed with steroids or thyroid replacement seems to be somewhat, as comparison, favorable to the side effects of cystectomy.

DR. HOFFMAN: Dr. Siddiqui, a follow-up?

DR. SIDDIQUI: I wanted to actually comment

on the random biopsy, the comment that had been made, because it's very much a urologist space, one. When I noticed it in the write-up, I actually spent a little bit of time just kind of looking into it. I'm not personally convinced that a lot of disease is being missed with the lack of random biopsy in cytology-negative patients in particular.

The reference, it was a good reference that was used in the write-up to come up with the 15 percent, but the 15 percent represents -- it came from a systemic review, and most of the studies that came up with that 15 percent would do random biopsies and a resection, and then look at -- the random biopsy would be from areas that look normal, and then you just look at how often is the normal-looking biopsy actually positive for cancer. But that doesn't take into account the fact that many of those patients actually had visible lesions, so we're not going to be missed, per se.

So 15 percent does not mean 15 percent like missed disease, perhaps; it just means that when normal-looking tissue is biopsied in a patient, 15

percent of the time it has cancer. As far as I can tell, the actual missed rate is probably closer to 5 percent, based on the literature I could find. I found two studies, both said 5 percent, so as far as I'm concerned, it's gold. But I think this is a topic that's going to be hard to come up with the concrete numbers, but that's the one thing that I thought I would comment on there.

DR. HOFFMAN: Dr. Klepin?

DR. KLEPIN: Thanks. Heidi Klepin. I just wanted to add more to the conflict I suppose. As we think about risk and benefits, I think some of the things that we're struggling with is that we all like to think that avoiding or delaying surgery as morbid as we know that it can be, would be a quality-of-life advantage for our patients; although we don't necessarily have the data from this study and from the study design to tell us that, but I could certainly believe that, although we do have the concerns around, now we've taken let's say a 75-year-old patient who may still have -- take their cancer out of the picture -- a

10-year life expectancy, but we've moved them a year or two down the road, and many of them are still going to be moving towards surgery. At that point, they may have some acquired comorbidities, so are we then increasing some risk with their ultimate surgical procedure? That was raised.

I think if we think about that in the context of the patient population, we know that these are older adults. So I think from that standpoint, the data gives us some good information that at least approximates the patient population. It would have been nice to see the actual details of the comorbidity profile so we could put that into context and say are these really the patients that I would be seeing in clinic?

We know their performance status was fairly good, PS 0 to 1 majority, so if this moves into clinical practice, we could expect that you're going to have patients who are getting this treatment, who have a performance status that may be a little bit worse than what we're seeing in the clinical trial, with perhaps more comorbidity, and

certainly patients are going to -- I would say from my experience as a medical oncologist, they're going to be very interested in being able to take an immunotherapy option over going to surgery.

So just thinking about who's going to be getting the treatment, do we have a handle on what that toxicity profile would look like in this patient population and what the tradeoff might be? Not necessarily. So I just want to throw that out there as more conflict for us to ponder.

DR. HOFFMAN: Dr. Apolo?

DR. APOLO: I have a question for my urology colleagues. It was mentioned the blue light versus the white light, and the majority of the patients on this trial underwent white light for detection of CIS. I think it was 94 percent that was quoted.

Is there a concern about the results and the outcomes? Would you think that the data would look different if blue light were used? I guess we would detect more CIS in all the patients, but is that a concern that you have?

DR. AGARWAL: I think what we probably would

have seen is a lower 3-month CR rate, and we probably would have seen that maybe the response and duration of therapy may be a little bit shorter because you'd pick up CIS at an earlier time point. But the reality is not everybody has blue lights. It's an expensive technology and you're doing a multicenter trial. It's hard to mandate that everybody has that, but I think that you would be more likely to pick it up.

So you could argue that this was a real-world trial, so in a real world, most patients are going to get white light cystoscopy, so we have to base it on what's in the real world. But in the context of a trial to really determine whether or not to approve a drug, I think that fact is not lost; that without blue light, the rates may be more favorable than they would have been had blue light been used in a greater number of patients.

DR. HOFFMAN: Dr. Cristofanilli?

DR. CRISTOFANILLI: I appreciate the comments from the urologists. The way that we see this disease is from the moment of the diagnosis of

this microinvasive invasive disease, you already have fast death moment for a curative intent. But before that, you are trying to delay the inevitable that is essentially the cystectomy, so I think BCG is already the first step.

I'm trying to see this in the context of this intervention, where you can delay for a long time the inevitable. So if you think this is the most aggressive, the one that has no response to BCG, I think about the group of patients that start with BCG, and they may respond or not respond. If you don't respond, obviously you go to this intervention. Can you delay cystectomy that is associated with morbidity, significant morbidity, for 3 to 5 years?

Maybe this, overall, will eventually improve not only the quality of life but certainly the survival of these patients, and maybe the next step would be to compare BCG with a systemic therapy, with pembrolizumab, to see if we can extend the benefit or reduce the resistance because immune intervention seems to be effective. So to not look

at the specific small interval of this study, but at the big picture, to me, it seems to be very important.

DR. HOFFMAN: Dr. Hinrichs?

DR. HINRICHS: I think I'm comfortable that I understand the toxicities of pembrolizumab in this setting. Everyone says their drug's well tolerated, but this one actually is well tolerated. I think I also understand the downsides of cystectomy, and it's a pretty awful procedure. Where I'm a little less certain is what sort of benefit the patient experiences from this drug when it works. That's something that as someone who doesn't see these patients on a daily basis, I think we really need input from the urologists to tell us if this is beneficial.

The other comment that I have is that we're asking about the use of this drug in the setting of one unresectable disease. So in that setting, keep in mind that there is no dichotomy here going against or delaying surgery. This is where surgery is not possible; so that is one part of the

question.

Then the other part of the question is whether there should be an option for patients to receive this systemic therapy, granted they're likely to eventually come to needing a cystectomy, but should the patient have the option to choose that treatment after being informed of how this will probably play out? It's not like we're deciding, okay, now everyone has to have pembro before they get a cystectomy; we're asking should this be a discussion that we have with patients and an option that we offer them?

DR. HOFFMAN: Dr. Murdock?

DR. MURDOCK: I'm trying to think in my mind what the discussion would be like, and it would be something like, well, you have a 19 percent chance of delaying your cystectomy for some amount of time, and then there might be -- I don't think we understand from this study, but we might ultimately have something like a 10 percent chance or some 5 to 18 percent chance of having an actual cure in some of these people. We don't know from this

study. I think that's the way people are interpreting it, that we just don't know.

So then we're going to say to them, there's a 19 percent chance that you're going to delay cystectomy for some number of months, 1-plus years or 2 years, and then we're going to be leaving them with the option of either doing that or going ahead with cystectomy. I'm wondering how many of those patients are going to choose the pembro.

I think some of it will depend on whether we can really say there's a certain percent of you who really will be cured, and that's what I'm kind of struggling with because the data here doesn't really tell you that even 10 percent of the people will actually be cured of their CIS. Maybe I'm not understanding it. Maybe someone has a better understanding of the data than me.

DR. HOFFMAN: A follow-up, Dr. Siddiqui?

DR. SIDDIQUI: Yes. I'm going to echo off that. I would expect that the urologic community would, in general, incorporate this as an option with evidence -- relation of risk and benefits

based on the patient. We already do that with, say, for high-grade T1 bladder cancer, not part of this purview right now. But for [indiscernible] high-grade T1, you often will either do BCG, which has a 60-70 percent response rate, or in some select cases cystectomy for someone who's healthier and just has the right profile for getting a cystectomy.

So I think that that's already built into the thought process. Even at earlier stages in aggressive cancers, I would imagine that someone who's healthy and a good cystectomy candidate, you would discuss with them BCG refractory disease. At this point, I'm kind of just repeating what you said, but a 20 percent, or whatever the literature ends up quoting as the response rate, versus a cystectomy right now, what do you want to do? Someone who's not a good cystectomy candidate, it would make a lot more sense to keep going down this road.

DR. HOFFMAN: Dr. Agarwal?

DR. AGARWAL: I think my one fear is

probably the discussion will be very similar like we did with valrubicin, where we know after a year, a majority of patients will not respond from it. So we'll probably give the drug to our sickest patients who are reluctant to pursue surgery and we're reluctant to offer surgery because we don't think they would survive it.

I think this may fit in that space, and I'm eager to see what combination studies with this drug and with other intravesical agents show over time, because I do feel like this study at least is giving us -- it's answering the question, what is the response rate in BCG unresponsive, high-risk, non-muscle invasive bladder cancer? Before this trial, we didn't have that data, and now we have real-world data showing what a number is.

I guess, again, I'm so conflicted whether that number is high enough to go forward, but I do think this will probably not open the flood gates. I don't think most patients will probably jump on this therapy, but I do think it will probably find a spot for the right patient.

DR. HOFFMAN: Dr. Uldrick? Oh, I'm sorry. Dr. Pavlovich?

DR. PAVLOVICH: So a little bit addressing your comment about BCG, obviously this is now this BCG unresponsive cohort, so it's a little bit different. Although we try BCG, we try maintenance BCG, we try second induction BCG, we're kind of beyond that here for this subset of very difficult patients. But BCG has been shown, as you say, to delay progression of disease, and it can be years of delay. So one can take the 82-year-old chronic lung patient with this and push him off into never having a cystectomy, and he passes away of something else. In that sense, BCG is a big success in avoiding a cystectomy in that kind of comorbid patient.

I don't think delays of whatever, 3 to 9 months, are going to be as helpful. And again, in this very refractory, unresponsive population -- and I said this before -- I am concerned we're just letting the disease fester, and get into the muscle, and make the cystectomy

less curative. Because the earlier you do the cystectomy in high-risk patients, the earlier it is the only therapy they'll need. I mean, they're not all cured, but certainly more than 10 to 19 percent.

Another comment I would make is that we're forgetting a little bit, given that this is kind of a med-onc setting, that surgery does play a role here. And all of these patients are getting biopsies and resections, and there are a very small minority patients, even in this high-risk subgroup, that over time, whether they stop smoking, they start drinking more water, they take yoga, and they get lots of aggressive biopsies and fulgurations, they actually clear their disease, at least for some period of time; no pembrolizumab involved.

In that 19 percent, that one year, there may well be some who were fortunate, who were treated by a great urologist who did something to their life, whatever. Of that 19 percent, some handful may have just been cleared by fulguration; some, the recurrences within that group are missed

because of the blue light issue; some didn't have random biopsies, and they may have missed one there; and some of the others would have had low-grade recurrences because, again, we're just looking at the high-grade recurrence. I believe, at the 3-month and 12-month time points. We're forgetting about all the patients who are still getting transurethral resections.

So again, it goes back to what have we gained with this medication. It's becoming a very small gain in my mind, but I'm willing to -- and, to me, all these immune-related side effects are real and possibly serious. We're down to single-digit responders; how about single-digit severe adverse events?

DR. HOFFMAN: Dr. Klepin? Do you have a comment?

(Dr. Klepin gestures no.)

DR. HOFFMAN: Okay. Well, I actually take your point -- Philip Hoffman -- about the immune adverse events. And again, my frame of reference is with a different patient population, but I guess

my experience with them is not that they get a short course of steroids and then they're back to how they were, especially elderly people who can rather quickly get proximal myopathy from steroids, and then they're weaker, and then it's hard to get them off the steroids, and you put them back. So sometimes they've had a nice CR to whatever cancer they have, but can't really take advantage of that time.

So again, most of the time, I think we all agree that certainly compared to aggressive chemotherapy, most of the time immunotherapy is much easier, except when it's not, and it's not predictable when it's not.

Dr. Kraus?

DR. KRAUS: Just a follow-up to the conversation because it's very interesting to hear the positioning of the benefit. It's striking to me, though I'm not quite clear on it, what appears to be the wide use of non-cystectomy therapies of various sorts after this trial, as well as it sounds like in general in practice. So I'm

wondering how much is a differential between the community and large institutions, and is the trial representative or not.

But if there's that wide use, why is there that wide use if there's not much benefit to these things, these agents that seem to have less defined benefit-risk than pembrolizumab that we're talking about now, if I'm understanding correctly? But I'm just throwing that out for discussion because it's a little troubling if many people are using all these different agents that, for the most part, may not be approved.

The one approved agent, intravesicular, probably has white-light response rates and durations that seem not as good as this agent. To me, a 3-month response rate is probably less than what would happen if somebody got observed and treated longer, so it may be higher, perhaps, if we look at the history of other settings with immunotherapy.

So just help me with that context of all these other therapies being used, not cystectomy in

the community, and what the benefit-risk is there and what's going on.

DR. HOFFMAN: Dr. Siddiqui, do you want to respond?

DR. SIDDIQUI: I think that it just reflects that there's a lot of conflicting data out there, so there's a combination of things. Some of these things are different investigational drugs even, so most likely reflecting centers that had access to numerous trials to feed patients into. Some of these patients got BCG again, which just reflects, I think, a desire to help the patient without many tools to help them with. That's probably what it comes down to.

DR. HOFFMAN: Dr. Agarwal?

DR. AGARWAL: There's also emerging intravesical treatments out there with encouraging data that I would say would be in line with what we're seeing here. There's also regimens that are practiced by a lot of institutions, specifically intravesical chemotherapies in various combinations, especially given the BCG shortage,

not only for BCG-naive patients but BCG unresponsive, high-risk patients that are showing, again, if you look at the emerging data, the response rates are looking similar over a short window of 12 months.

The problem is that there is no agent in this space, so patients desperately don't want their bladders removed, so they're willing to try various therapies, and their urologists are willing to go wrong with that. But, unfortunately, sometimes we miss the opportunity to offer cystectomy in a timely fashion to prevent progression. I think it speaks to the fact that we are so heavily dependent on BCG, and with its shortage, it's created this freedom to give a variety of intravesical agents, and that's extending not only in the naive space but in the unresponsive space as well.

DR. HOFFMAN: Dr. Murdock?

DR. MURDOCK: I think the one thing that today has shown. more well than anything else, is that it is safe to delay the cystectomy, although

Dr. Pavlovich is saying, well, I don't know if it's safe to delay the cystectomy. But from the data presented, when you look at the cystectomy specimen, only 3 patients have progression and the vast majority have a lot less disease than you would otherwise expect.

So as opposed to a lot of other agents like this, systemic agents that are kind of hit or miss where, say, two-thirds of patient groups it does well with, and the other third, there's progression under your nose, this is not like that. And I think that is a good thing because at least we don't have to ask ourselves if we give the drug, whether we're missing the window to do the cystectomy.

DR. HOFFMAN: Dr. Siddiqui?

DR. SIDDIQUI: This is something I was hoping I'd get people's thoughts on because I'm having a really hard time wrapping my head around it. The FDA AUA had a combined panel some years ago where the group of experts came together to try to come up with meaningful guidance for this exact

disease process, and the numbers they came up with were a 6-month complete response rate of 40 to 50 percent and a 18 month response rate of 30 percent, which this trial did not meet.

So if you think of it from that perspective, I'm kind of like it falls short of that expert's opinion on what is a clinically significant response; I think they phrased it that way. But then if you look at this question very specifically -- at least when I look at it, do you observe the complete response and duration represent a favorable risk-benefit profile -- it's not necessarily hitting on a clinically meaningful response. And this drug does represent an improvement on the only FDA-approved treatment out there right now for this disease, valrubicin.

So I'm having a hard time kind of reconciling how much to think about the prior expert recommendation of a target, which I'm not sure it's proven and may be too ambitious and too aggressive versus to compare this to what's out there right now.

DR. HOFFMAN: Dr. Hinrichs?

DR. HINRICHS: I'll try to jump into this. I get the point of setting kind of target response rates, and I understand why that would be an important topic for discussion. I also think that they have to be taken in context because you can't just say the response rate has to be this without considering the toxicity profile of the treatment.

So if you're talking about a highly toxic systemic therapy, then you need a certain response rate for that to make sense. Even if you're talking about local therapies, they do have downsides associated with them, too, and you have to talk about response rates that make sense in the context of that.

So while these numbers are kind of interesting to consider, I think that they can't be held to absolute, and they need to be considered in the context that they're being discussed. I guess that's just my take on what to make of those numbers.

DR. HOFFMAN: Dr. Beaver?

DR. BEAVER: Hi. Julia Beaver, FDA. To touch on this issue of does FDA consider this a benchmark, I know you keep coming back to that. We do not consider that a benchmark or we wouldn't have brought this before an advisory committee to get your input to the question at hand.

DR. HOFFMAN: I think we should end the discussion and proceed to the vote. We'll be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you're 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'll go around the room and each individual who voted will state their name and vote into the record.

You can also state the reason why you voted as you did if you want to. So let's go ahead and vote.

(Voting.)

DR. HOTAKI: It looks like we're waiting for one more person to vote. Everyone needs to push their vote again just to make sure they all registered. We're Waiting on one more vote. Again, if everyone can just push their vote one more time. You're voting. The only person that's non-voting is Dr. Kraus.

We have everyone now? For the record, the vote is 9 yeses, 4 nos, zero abstentions.

DR. HOFFMAN: Now that the vote is complete, we'll go around the table and have everyone who voted state their name, their vote, and if you want to, you can say the reason why you voted as you did into the record. Let's start on the left. Dr. Apolo?

DR. APOLO: Andrea Apolo. I voted no. I struggled with this because my patients need better treatments. But I think the data is still early, and we need longer follow-up in order to put this

into standard treatment options for patients with non-muscle invasive disease.

DR. HOFFMAN: Dr. Klepin?

DR. KLEPIN: Heidi Klepin. I voted yes. I primarily voted yes because I feel like the response data that was presented I felt was clinically meaningful for this patient population and represents an advance, a new option that appears to be better for those patients particularly interested in delaying or avoiding cystectomy for as long as possible or may be poor candidates, which represents a large proportion of the patient population of older adults.

I was reassured by the data that suggested that the disease didn't appear to be progressing rapidly during that time frame, at least based on the data that we saw. I would like to have seen some additional data that would be able to answer the question for our patients about would there be any additional downsides with respect to toxicity and side effect.

It would be nice to have, if this is

approved, postmarketing data, looking at outcomes, particularly for those patients who go on to cystectomy to see if we can see any signals for any adverse events in that setting since this patient population is different than those that would be getting these treatments in the neoadjuvant setting.

DR. HOFFMAN: Dr. Hinrichs?

DR. HINRICHS: Christian Hinrichs. I voted yes. The drug is safe, and it does seem to be effective for these patients and have a role in the treatment of a particular situation. I also think I have a lot of confidence in the physicians counseling these patients to present this as an option and to present it in the context of what's known and not known for the patients and the doctors to make good decisions about this treatment. Otherwise, I think Dr. Klepin summarized nicely my thoughts on it, too.

DR. HOFFMAN: Dr. Halabi?

DR. HALABI: Susan Halabi. I voted no. Although the study was well designed and it met its

primary endpoint, I struggled with interpreting the data. There were some groups where there wasn't clear benefit, even though the sample size was small. Also, a lot of information was missing. I would have liked to see more data presented and quality-of-life data.

Again, this was a difficult decision because I've been on the fence since I've read this application. Again, I wish there is no binary decision, but unfortunately the FDA will stick with a binary decision.

DR. HOFFMAN: I'm Philip Hoffman. I voted no. I definitely was very much on the fence, and I think I expressed my internal conflicts. I think for a disease that is usually slow over time, I didn't find it sufficiently compelling to have a relatively short duration of benefit and the concern about using admittedly mostly safe but somewhat unpredictable systemic therapy for a local disease, for which we certainly need better local therapies. But altogether, I came down on the negative side of the fence.

DR. CRISTOFANILLI: Dr. Cristofanilli. I voted yes. This is a difficult population, high-risk population, and this obviously was an important study to run. It's not a definitive final therapy, but clearly improves. So it gives another option, as was mentioned to these patients, if they want to delay their cystectomy. Probably we need to learn a little bit more about which patient will get even more benefit or longer benefit, and even if you get in an earlier setting, BCG or immunotherapy certainly are effective.

Again, this builds on the evidence in advanced disease, so this drug is affecting advanced disease and now moving in a different setting and is relatively safe. We treat these patients, different patients obviously, with immunotherapy, and we see this every day.

DR. ULDRICK: Thomas Uldrick. I voted yes. I was also convinced by the response rate and think that this offers a potential option for patients who are not good surgical candidates. I think the data is a little immature to see the long-term

durable response in what is currently about 20 percent of patients, and I think additional data could be helpful to inform the discussion around whether this is a replacement for a cystectomy in a portion of patients as well.

DR. HAWKINS: Randy Hawkins. I voted yes. Again, I thought initially I would say yes, and then I said no. And as I got some advice from colleagues, I felt comfortable with yes. I think that patient control is important, that the patient be able to say yes or no, I want this, I want that, if there's not excess of harm. I was helped by the fact that the folks who use this type of therapy regularly say these side effects are manageable, they really are, so I felt better about that balancing part.

I think that the urologists need other things in their toolkit, but I think all those people involved in this patient care are going to have to flex their brains to really have a discussion around informed decision. I don't think it's going to be an easy decision. I think it's

going to be difficult to have that kind of decision. Sometimes in private practice, we repeat the things we're saying again and again to make sure people will understand what we're saying, and I think this is one we have to be careful how we present it to our patients, but I voted yes.

MS. JOHNSTON: Colette Johnston. I'm the patient advocate, and I voted yes. I do feel like our safety concerns were met on this drug, and I do realize that the majority of this patient population that we consider -- and I'm going to be very careful here -- elderly, I know some of these elderly people that I live with are very active, and this drug would offer them an option that they didn't have.

I think that they would be of a mindset and an ability to use their doctor's advice and make a decision for themselves personally that that was what they were wanting because the ultimate surgery for this is truly life altering for that patient population, that fits within this patient population. I do agree I would have liked more

data, and I think there's more to be learned on this, but, overall, I feel confident with the vote of yes.

DR. PAVLOVICH: Christian Pavlovich. I voted no. I think that, clearly, the drug has shown biologic activity in muscle-invasive bladder cancer. I'm not sure it really has shown that in non-muscle invasive disease in this BCG refractory or unresponsive population. I really looked at those two groups of bladder cancer experts that got together in the last decade to come up with benchmarks for what would be a clinically meaningful response, and this did not get close to those benchmarks, not close, and those people deal with bladder cancer every day, which few of us in this room do. So that's very much affected me in terms of my voting.

I think that there were some responders, and if we had more data on subsets, or PD-L1 staining, or something where we could identify who might respond and put the drug through for those kinds of patients, rather than for all patients in this

group, it would have gotten my vote, potentially. But at this point, I could not be convinced that we were doing anything of benefit to anything but a very, very small subset of these patients.

DR. AGARWAL: Piyush Agarwal. I voted yes. It was 51-49 in my head, and ultimately I was concerned a lot about some real-world problems that we are now going to face. This is already the most expensive cancer, and now it's going to get even more expensive. This is going to mean treatment issues for providers when the urologists engage as a medical oncologist and increase burden on our healthcare system.

But ultimately, I think what this does do is it establishes a benchmark for what a response should be in a BCG unresponsive population, which is a data point we never had.

Number two, it does provide patients with an alternative that may not be the right alternative for the majority of patients, but in some patients it may be. Then finally, I have a lot of faith that urologists will use this and advise patients

judiciously, but I have concerns, and I think what this will lead to is a slew of products coming to the FDA's door and probably a bunch of approvals down the road, and then hopefully the data will bear itself out, and we will choose the best agent that's available.

So I'm hoping we'll have an embarrassment of riches in the future, but right now, I feel like this is along the right track, but I, again, still remain conflicted.

DR. SIDDIQUI: Minhaj Siddiqui. I voted yes. Ultimately, it came down -- I think like Meneer [ph] is saying, it was a difficult decision, and it really came down to the fact that where we're at right now with many patients, they need something, and this would make a lot of sense for them, even understanding that the lack of efficacy relative to the ideal exists with this. I think it will just be absolutely imperative in our field to, should this be approved, responsibly use this in the right patient population.

But I feel like our field does do that, that

there is risk stratification and personalized decision making. And the hope that I voted with was that this would be incorporated into that pathway and used in select patients as appropriate, and those patients, I feel like this could really benefit them.

DR. MURDOCK: I'm Jonah Murdock, and I voted yes. I think this is a difficult decision. Like many were saying, it's not a slam-dunk. I voted yes because the drug appears to be safe and because it may help up to 19 percent of patients delay, for quite a while, cystectomy, or not have one at all. I think we need to know more information about those 19 percent and see how durable the response is for them.

DR. SUZMAN: Daniel Suzman, FDA. I'd like to thank the committee for their consideration and discussion. Before we adjourn, I did want to get the committee and the sponsor's input on our pilot briefing document, what they felt worked, what they felt didn't, what was missing, and so forth.

DR. HOFFMAN: Before we get to that, I'll

just briefly summarize. The vote, as we said, is 9 to 4. I think that many of the yes votes were maybe 60-40 and the no votes were 40-60. I think that there is a lot of conflict, and I think that probably a lot of this will be satisfied over time as more data comes along.

I think there were concerns about the follow-up time, the question of are patients going to be getting cystectomies anyway, so is it worthwhile to have delayed that? In general, the drug is quite safe, but there are some potential risks.

A couple have raised the concern about whether the AUA and FDA guidance was met or not, and we've heard that perhaps that wasn't intended to be a fixed benchmark, but a benchmark nonetheless; and, again, how much activity does this have and how great will be the effect in the long run. I think everyone has been up front and articulate about their concerns and their conflicts, and here we have the final vote.

What we're being asked here by Dr. Suzman

is, as I'm sure you noticed, the briefing document that we got in advance, as compared to in the past where we had two sets of documents, one from the applicant and one from the FDA, this was presented on a single document the applicant's points in a paragraph followed by the FDA's points relative to that specific issue in a paragraph.

Am I saying that right?

DR. PAZDUR: In general, yes. But here again, the data was presented in the document.

DR. HOFFMAN: Oh, yes.

DR. PAZDUR: What the issue here is, is we really wanted to avoid duplication here, and we found out, through really years of looking at these documents, that there was a tremendous amount of duplication. And because there were two documents, frequently the important issues were lost, basically, because you have two documents that weren't talking to each other.

So what we hope by having this is more of a point-counterpoint thing, where people could capitalize on the points of contention here rather

than getting lost in kind of the minutia, so to speak, because, here again, it's a briefing document. It's not the be-all and end-all or a treatise on the drug.

Here again, that's why we're asking people what their feeling on it is. It's a pilot that we're doing from the Oncology Center of Excellence, but it is a pilot, and we're very interested in hearing, especially those of you that have been on the committee for some time and had exposure to other briefing documents, your experience with it and likewise from the company, their experience.

DR. HOFFMAN: I for one welcomed it. I think the documents in the past are very lengthy, and the notion of "briefing" documents, if I can use the term, was welcomed. But also, I think it helps to focus on the individual issues, and not, well, here's 100 pages from the applicant and 60 pages from the FDA, and are we sure that we're addressing the question or addressing the point that's being made by the applicant.

I welcome other comments.

DR. CRISTOFANILLI: I think it's more efficient for us to review a document that's summarized and point us out to discussion. The review has been done just looking at 200 pages of documents that repeat natural history, drug characteristics, and so forth.

DR. HALABI: I actually agree with what's been said, and actually, that was my first application I reviewed, and I was expecting the others to be the same way; so I welcome the innovative briefing document. Hopefully, it will become the norm.

DR. PAZDUR: Does the company want to comment on it? I know you interacted with the division on this while you were doing the document, and I'd be interested in hearing your issues with it, if any.

DR. EBBINGHAUS: Merck overall thought that it was a very efficient process. We appreciated the ability to interact with the agency and identify what the core issues were, so I thought it was a very efficient process. The one potential

tweak or whatever might be, sometimes there's information that panelists may want that FDA and the sponsor may think are less important. For example, quality-of-life data could have been included, but we came to a mutual agreement not to in this case.

So that's the only thing I would say that, probably, if we had independent documents, we would have erred on the side of including it, not because we think it's highly reliable data, but just because people ask about it commonly, and they want to see it. But otherwise, I think it was a very efficient process. We appreciated it, and I think it's a keeper.

DR. HOFFMAN: Any dissenting votes?

DR. KLEPIN: I'm not dissenting, but I was just going to -- I liked the format, and I agree with what everybody said. I would just add, though, as a reviewer, I did like in the past having some of that detailed quality-of-life data, even with all of its challenges.

DR. PAZDUR: Here again, it wasn't meant to

eliminate any quality-of-life data.

DR. KLEPIN: Yes. Things like that could be added at the end --

DR. PAZDUR: That's a good point that we could bring back --

DR. KLEPIN: -- as an appendix or something.

DR. PAZDUR: -- into the document. And here again, we have problems of the single-arm nature of the trial preventing, really, an adequate interpretation of a lot of the quality-of-life data, too.

DR. HOFFMAN: Ms. Johnston?

MS. JOHNSTON: I would echo that also. The quality of life was the one thing I felt like was really missing for me as an advocate. I like to see a little more of that data in there.

Adjournment

DR. HOFFMAN: We will now adjourn the meeting. Panel members, we request that you leave your name badge here on the table so it can be recycled, and please take all your personal belongings with you because the room will be

cleaned at the end of the day. Anything you leave on the table will be disposed of. Thank you.

(Whereupon, at 4:36 p.m., the afternoon session was adjourned.)