

1 FOOD AND DRUG ADMINISTRATION
2 CENTER FOR DRUG EVALUATION AND RESEARCH

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4
5 ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING
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8
9 Tuesday, December 17, 2019
10

11 Afternoon Session
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13 1:00 p.m. to 4:36 p.m.
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18 FDA White Oak Campus
19 White Oak Conference Center
20 Building 31, The Great Room
21 10903 New Hampshire Avenue
22 Silver Spring, Maryland

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C O N T E N T S		
1	AGENDA ITEM	PAGE
2	Call to Order and Introduction of Committee	
3	Philip Hoffman, MD	12
4	Conflict of Interest Statement	
5	Lauren Tesh Hotaki, PharmD, BCPS, BCIDP	15
6	FDA Opening Remarks	
7	Daniel Suzman, MD	20
8	Applicant Presentations - Merck Sharpe & Dohme	
9	Introduction	
10	Jeffrey Stuart, PhD	28
11	Unmet Need	
12	Gary Steinberg, MD	34
13	Efficacy and Safety	
14	Ekta Kapadia, MD	45
15	Clinical Perspective	
16	Ashish Kamat, MD, MBBS, FACS	63
17	Benefit-Risk	
18	Scot Ebbinghaus, MD	68
19	FDA Presentation	
20	Keytruda (pembrolizumab)	
21	Jamie Brewer, MD	71
22		

	C O N T E N T S (continued)	
	AGENDA ITEM	PAGE
1		
2		
3	Clarifying Questions to Presenters	88
4	Open Public Hearing	123
5	Questions to the Committee and Discussion	131
6	Adjournment	180
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
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1 P R O C E E D I N G S

2 (1:00 p.m.)

3 **Call to Order**

4 **Introduction of Committee**

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

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

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

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

1 DR. SUZMAN: Daniel Suzman, clinical team
2 lead.

3 DR. BREWER: Jamie Brewer, clinical
4 reviewer.

5 DR. CHENG: Joyce Cheng, statistical
6 reviewer.

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

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

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

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

15 DR. HOTAKI: Lauren Hotaki, designated
16 federal officer.

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

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

22 DR. ULDRICK: Thomas Uldrick, medical

1 oncology, Fred Hutchinson Cancer Research Center.

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

5 MS. JOHNSTON: Colette Johnston, patient
6 advocate.

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

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

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

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

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

17 DR. HOFFMAN: Thank you.

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

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

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

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

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

21 **Conflict of Interest Statement**

22 DR. HOTAKI: The Food and Drug

1 Administration is convening today's meeting of the
2 Oncologic Drugs Advisory Committee under the
3 authority of the Federal Advisory Committee Act of
4 1972. With the exception of the industry
5 representative, all members and temporary voting
6 members of the committee are special government
7 employees or regular federal employees from other
8 agencies and are subject to federal conflict of
9 interest laws and regulations.

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

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

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

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

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

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

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

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

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

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

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

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

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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

1 cases and is generally stratified based on stage,
2 grade, histology, and prior therapy into low,
3 intermediate, and high-risk groups that reflect the
4 risk of recurrence or progression to
5 muscle-invasive or metastatic disease. High risk
6 non-muscle invasive bladder cancer carries a
7 particularly poor prognosis with at least a
8 20 percent risk of progression to muscle invasion
9 and 14 percent risk of death from bladder cancer,
10 with the majority of these events occurring within
11 4 years.

12 A standard of care treatment for
13 intermediate and high-risk, non-muscle invasive
14 bladder cancer is intravesical BCG therapy.
15 Following persistence of disease or recurrence
16 after BCG, radical cystectomy is generally
17 considered the standard of care. However, radical
18 cystectomy is associated with high risk of
19 postoperative complications and mortality, with
20 90-day mortality rates up to 7 to 15 percent in
21 some series, depending on patient age and
22 comorbidities and the cystectomy case volume of the

1 surgeon and center.

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

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

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

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

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

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

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

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

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

22 With the removal of these 6 patients, the

1 FDA is considering the remaining 96 patients to be
2 the primary efficacy population. The safety
3 population remains unchanged. The complete
4 response rate was 41 percent based on evaluation at
5 3 months. While a data cutoff of May 24, 2019 was
6 used for all analyses of progression and safety, an
7 updated data cutoff of September 24th was used to
8 update only duration of response outcomes.

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

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

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

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

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

1 the sponsor's and FDA's presentations.

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

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

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

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

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

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

18 We will now proceed with the applicant's
19 presentations.

20 **Applicant Presentation - Jeffrey Stuart**

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

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

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

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

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

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

12 This diagram contains registration trials in
13 the bladder cancer space, shown here from the least
14 to the most invasive cancers as we move from right
15 to left. We have an extensive development program
16 in muscle invasive and metastatic disease.

17 KEYNOTE-045 and KEYNOTE-052 are the pivotal trials
18 that led to the approval of pembrolizumab in
19 metastatic urothelial carcinoma in 2017. We have
20 two trials in the non-muscle invasive bladder
21 cancer space, shown on the far right.

22 The trial we will focus on today is KEYNOTE-

1 057, investigating pembrolizumab monotherapy in
2 patients with BCG unresponsive, high-risk,
3 non-muscle invasive bladder cancer with carcinoma
4 in situ. In total, this illustrates Merck's deep
5 commitment to developing and registering new
6 therapies for patients with urothelial cancer who
7 are in need of improved treatment options.

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

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

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

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

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

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

11 The safety profile has been extensively
12 documented across multiple tumor types with over
13 30,000 patients treated worldwide in clinical
14 trials. The experience in KEYNOTE-057 was
15 consistent with other studies using pembrolizumab.
16 Therefore, pembrolizumab offers the opportunity for
17 patients to experience a complete and durable
18 response and preservation of their bladder without
19 undue risk of cancer progression.

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

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

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

16 **Applicant Presentation - Gary Steinberg**

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

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

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

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

1 this patient population.

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

9 Circled on this illustration are the
10 different stages of NMIBC, Tis, carcinoma in situ,
11 or CIS, which is restricted to the urothelial
12 lining and often diffuse and patchy in nature, and
13 thus is difficult to fully resect. Papillary
14 tumors present as discrete lesions and can be
15 noninvasive noted as Ta, or can be invasive to the
16 lamina propria, noted as T1. Papillary tumors can
17 be fully resected. CIS and papillary tumors often
18 occur concomitantly.

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

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

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

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

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

4 How was CIS initially diagnosed and treated?

5 The standard for treatment for CIS, plus or minus
6 papillary disease, is TURBT to fully resect
7 papillary lesions, remembering that CIS is not
8 fully resectable, followed by intravesical BCG
9 immunotherapy for up to 3 years.

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

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

1 of progression in a BCG unresponsive CIS population
2 is difficult.

3 However, literature reports and all
4 high-risk, non-muscle invasive bladder cancer that
5 utilize various definitions of BCG failure indicate
6 that progression to muscle invasive disease will
7 occur in 20 to 40 percent of patients within
8 5 years, and metastatic disease will occur in up to
9 50 percent of individuals who progress to muscle
10 invasive bladder cancer with death due to bladder
11 cancer in nearly all of these cases.

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

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

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

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

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

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

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

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

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

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

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

19 The FDA and the AUA convened a workshop in
20 2013 to spur clinical development of new therapies
21 in NMIBC. Importantly, a framework for the design
22 of clinical trials in the BCG unresponsive setting

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

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

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

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

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

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

3 **Applicant Presentation - Ekta Kapadia**

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

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

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

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

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

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

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

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

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

18 All patients received pembrolizumab every
19 3 weeks for up to 2 years and underwent efficacy
20 evaluations to assess initial complete response
21 rate and duration of response for up to 5 years.
22 Those patients with a continued complete response

1 were permitted to discontinue pembrolizumab after
2 18 months.

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

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

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

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

7 The key efficacy endpoints in KEYNOTE-057
8 are consistent with the FDA guidance as well. The
9 primary endpoint in Cohort A was the complete
10 response rate of high-risk NMIBC, which was
11 evaluated using the exact binomial method,
12 comparing the lower bound of the 95 percent
13 confidence interval to the historical control rate
14 of 20 percent. This historical control rate was
15 based on the valrubicin complete response rate of
16 18 percent, which as you heard from Dr. Steinberg
17 was based on a heterogeneous patient population.

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

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

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

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

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

1 of the bladder and prosthetic urethra in males was
2 required.

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

13 I will now summarize the efficacy outcomes
14 of KEYNOTE-057 Cohort A, which again consisted of
15 patients with carcinoma in situ with or without
16 papillary tumors at baseline. In Cohort A, a total
17 of 102 patients were treated with pembrolizumab,
18 and this represents the safety population. Of
19 these 102 patients, 5 patients did not meet the
20 2018 FDA definition for BCG unresponsive disease,
21 and one patient was misclassified to Cohort A due
22 to a vendor transcription error. These patients

1 were excluded from the efficacy population. All
2 efficacy analyses, therefore, are based on an N of
3 96 patients.

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

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

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

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

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

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

1 pembrolizumab, based on study-specified disease
2 assessments.

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

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

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

1 3 months. The Y-axis shows the percent of patients
2 among the initial 39 who were remaining in CR. The
3 median duration of response was 16.2 months based
4 upon Kaplan-Meier estimates. However, it's
5 important to remember that this, again, is measured
6 from the time initial CR was achieved.

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

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

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

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

1 that pembrolizumab did not limit the opportunity
2 for subsequent treatments.

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

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

22 In summary, KEYNOTE-057 is a well-conducted

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

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

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

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

4 I will now move on to the presentation of
5 safety data from KEYNOTE-057. The safety profile
6 of pembrolizumab is well characterized, based on
7 the large clinical program that includes more than
8 30,000 patients who are treated in clinical trials
9 and the extensive postmarketing experience in
10 nearly 300,000 patients worldwide, who have
11 received pembrolizumab.

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

22 Here you see the overall safety summary for

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

6 As you can see, the majority of AEs were low
7 grade. Of the 26 patients with serious adverse
8 events, only 8 had treatment-related serious
9 adverse events per investigator assessment.
10 Approximately 4 percent of patients discontinued
11 study treatment due to serious AEs, and there were
12 2 deaths due to adverse events reported. Both were
13 considered unrelated to pembrolizumab treatment.

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

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

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

14 The immune-mediated AEs reported in KEYNOTE-
15 057 were generally consistent with the
16 pembrolizumab reference safety data set. The most
17 common AEs were hypothyroidism and hyperthyroidism,
18 and all were grades 1 or 2. The majority of other
19 immune-mediated AEs occurred in one patient each.
20 The grades 3 to 4 immune-mediated AEs also occurred
21 in one patient each and included type 1 diabetes,
22 adrenal insufficiency, and a severe skin reaction.

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

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

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

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

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

5 **Applicant Presentation - Ashish Kamat**

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

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

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

3 Radical cystectomy, as you heard, is a
4 morbid procedure, with hospital stays as long as
5 7 to 10 days. It has a very high complication
6 rate, including 15 percent hybrid complications
7 such as bowel leak and ICU admissions.

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

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

22 Patients clearly want to be cured of their

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

12 This is where an agent such as pembrolizumab
13 comes in. Pembrolizumab was studied in the highest
14 risk BCG unresponsive CIS population, and in this
15 notoriously difficult-to-treat patient population,
16 it had a clinically meaningful response rate of
17 41 percent. Importantly, this response was
18 durable. The median response duration was over a
19 year at 16.2 months, and 46 percent of responders
20 had a response that lasted at least 12 months.

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

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

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

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

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

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

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

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

1 **Applicant Presentation - Scot Ebbinghaus**

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

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

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

14 Pembrolizumab provides direct evidence of
15 clinical benefit for patients with BCG unresponsive
16 CIS, as shown by a CR rate of approximately
17 41 percent. Importantly, these complete responses
18 last a long time. Based on Kaplan-Meier estimates,
19 the median duration of response is over 16 months
20 in KEYNOTE-057.

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

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

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

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

1 an informed decision not to undergo a radical
2 cystectomy.

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

6 DR. HOFFMAN: Thank you very much.

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

9 **FDA Presentation - Jamie Brewer**

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

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

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

11 During this presentation, we will briefly
12 discuss the available treatment for BCG
13 unresponsive, non-muscle invasive bladder cancer,
14 and discuss the key points of the FDA guidance
15 regarding trial design for this patient population.
16 We will review the efficacy and safety of KEYNOTE-
17 057 and provide a summary of the FDA position.

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

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

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

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

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

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

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

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

22 For patients with BCG refractory CIS, the

1 panel felt that an initial complete response rate
2 of 40 to 50 percent at 6 months and a durable
3 response rate of at least 30 percent for 18 to
4 24 months, with the lower bound of the 95 percent
5 confidence interval excluding 20 percent, could be
6 clinically meaningful.

7 The International Bladder Cancer Group has
8 also published its recommendations in 2016
9 regarding drug development in non-muscle invasive
10 bladder cancer, and stated that "For patients with
11 BCG unresponsive CIS, we recommend an initial CR
12 rate of 50 percent at 6 months and durable response
13 rates of 30 percent at 12 months and 25 percent at
14 18 months as clinically meaningful." These
15 recommendations were based on results of studies of
16 other salvage therapies in BCG refractory patients.

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

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

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

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

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

4 Although significant attention is paid to
5 the point estimate of the complete response rate,
6 the guidance states, "Clinically unimportant
7 complete response rates should be excluded from the
8 95 percent confidence interval." In addition,
9 random biopsies at prespecified time points are
10 recommended to ensure accuracy of documents of
11 complete responses but are not required.

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

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

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

15 The discussion of the efficacy of KEYNOTE-
16 057 is centered on Cohort A, as this is the
17 intended population described in the proposed
18 indication provided by the sponsor. The primary
19 efficacy endpoint for Cohort A was complete
20 response rate of high-risk, non-muscle invasive
21 bladder cancer, which included CIS with or without
22 high-grade Ta and T1 disease.

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

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

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

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

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

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

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

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

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

22 There was a minimum follow-up of 14 months

1 from the time of last patient enrollment to the
2 data cutoff, and a median duration of follow-up of
3 24 months. The median duration of response,
4 whether including or excluding recurrence of
5 low-grade disease, was 16.2 months with
6 approximately half of patients with complete
7 response having their responses persist for at
8 least 1 year.

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

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

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

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

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

22 Previous publications have reported that CIS

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

12 The primary safety population for KEYNOTE-
13 057 consisted of the full population enrolled to
14 Cohort A. Evaluation of safety included collection
15 of adverse events data; laboratory assessment;
16 patient narratives for deaths; serious adverse
17 events; discontinuations due to adverse events; and
18 adverse events of special interest; in addition to
19 an audit of case report forms.

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

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

6 There were 2 deaths on study that the FDA
7 did not consider related to pembrolizumab.

8 However, deaths due to pembrolizumab related
9 toxicity have been observed in other studies.

10 There were no events of progression to muscle
11 invasion or metastatic urothelial carcinoma on
12 study in Cohort A, with the minimum duration of
13 follow-up of 14 months and median of 24 months.

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

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

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

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

22 We agree that the observed rate of complete

1 response is substantially greater than that seen in
2 historical controls, including valrubicin. As of
3 the data cutoff, 19 percent of all treated patients
4 experienced the complete response of one year or
5 longer from the time of initial response, which may
6 be clinically meaningful. The median duration of
7 response was over 16 months with a small proportion
8 of responding patients still in response beyond
9 2 years.

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

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

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

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

12 **Clarifying Questions to Presenters**

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

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

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

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

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

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

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

5 DR. HOFFMAN: Dr. Cristofanilli?

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

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

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

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

14 DR. HOFFMAN: Dr. Pavlovich?

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

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

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

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

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

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

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

9 DR. STEINBERG: Correct.

10 DR. PAVLOVICH: Thank you.

11 DR. HOFFMAN: Dr. Klepin?

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

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

22 DR. KAPADIA: Given that the median age was

1 73 on KEYNOTE-057 and approximately 45 percent of
2 patients were 75 and older, a majority of patients
3 did have quite significant comorbidities coming on
4 to this study, which included cardiac as well as
5 renal disorders, as well as other -- like diabetes,
6 et cetera. We don't have an exact table listing
7 out all the comorbidities, but a majority of
8 patients did have comorbidities that you would
9 expect in an elderly population.

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

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

22 We have several trials evaluating

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

11 DR. HOFFMAN: Dr. Halabi?

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

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

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

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

1 patients who already had cystectomy?

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

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

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

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

1 the median duration of response.

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

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

14 DR. HOFFMAN: Dr. Kraus?

15 DR. KRAUS: It's really a follow-up question
16 to the response rate and the determination of CR at
17 3 months, I guess. If I remember the design, but
18 correct me if I'm wrong, it looked like patients
19 were mandatorily discontinued from therapy at
20 3 months if indeed they weren't responders.

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

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

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

18 DR. HOFFMAN: Dr. Agarwal?

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

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

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

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

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

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

4 DR. HOFFMAN: Dr. Siddiqui?

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

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

16 Can you clarify your question?

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

21 DR. EBBINGHAUS: Yes. None of those
22 3 patients had achieved an initial complete

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

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

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

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

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

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

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

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

14 DR. KAPADIA: Right.

15 DR. HOFFMAN: Okay.

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

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

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

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

9 DR. HOFFMAN: Oh, I'm sorry.

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

11 DR. HOFFMAN: Okay. Thank you.

12 Dr. Apolo?

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

22 DR. EBBINGHAUS: We have evaluated the

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

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

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

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

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

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

17 DR. HOFFMAN: Dr. Hinrichs?

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

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

3 DR. EBBINGHAUS: Yes, we did. We set a bar
4 that was intended to exclude an uninteresting
5 complete response rate. I'll just show this slide
6 again. So we prespecified that the lower bound of
7 the 95 percent confidence interval should exceed
8 20 percent, which it did in this trial.

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

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

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

22 DR. HOFFMAN: Dr. Hawkins?

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

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

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

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

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

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

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

8 DR. HOFFMAN: Dr. Pavlovich?

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

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

1 please.

2 DR. EBBINGHAUS: In general, the adverse
3 events in KEYNOTE-057 were quite similar to the
4 adverse events that we've seen across the program
5 and, in general, the adverse events resolved. The
6 one exception to that is with the endocrine
7 disorders. Endocrine disorders are often
8 long-lasting. We've only had data going for 5 or
9 6 years, so we can't use the word "permanent" but
10 they can be long-lasting and they may require
11 endocrine supplementation.

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

17 DR. HOFFMAN: Dr. Klepin?

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

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

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

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

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

7 DR. HOFFMAN: Dr. Apolo?

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

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

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

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

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

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

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

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

13 DR. HOFFMAN: Dr. Murdock?

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

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

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

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

22 DR. EBBINGHAUS: Time to cystectomy has not

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

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

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

22 Did I address your question, Dr. Hoffman?

1 (Dr. Hoffman gestures yes.)

2 DR. HOFFMAN: Dr. Apolo?

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

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

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

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

1 protocols and also with our product labeling.

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

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

9 DR. APOLO: That's better.

10 DR. WIVEL: Okay. Thank you.

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

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

19 (No response.)

20 DR. HOFFMAN: Okay. We'll now take a
21 15-minute break. We're a few minutes early.
22 Please remember that there should be no discussion

1 of the meeting topic during the break amongst
2 yourselves or with any member of the audience, and
3 why don't we plan to resume about 3:20.

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

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

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

14 At the time that we gathered and discussed
15 those numbers with the experts and the
16 statisticians, those numbers were not meant to be
17 hard benchmarks to compare any treatment outcome
18 against. They were more meant to help with the
19 statistical design and design of the clinical
20 trials. Clearly, in this study, the important
21 thing to remember is the responder analyses, the
22 41 percent response rate, and then 46 percent of

1 those responders had a durable response beyond
2 12 months; so the median duration response, 16.2
3 months.

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

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

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

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

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

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

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

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

4 **Open Public Hearing**

5 DR. HOFFMAN: Thank you.

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

13 For this reason, FDA encourages you, the
14 open public hearing speaker, at the beginning of
15 your written or oral statement to advise the
16 committee of any financial relationship that you
17 may have with the sponsor, its product, and, if
18 known, it's direct competitors. For example, this
19 financial information may include the sponsor's
20 payment of your travel, lodging, or other expenses
21 in connection with your attendance at the meeting.

22 Likewise, FDA encourages you at the

1 beginning of your statement to advise the committee
2 if you do not have any such financial
3 relationships. If you choose not to address this
4 issue of financial relationships at the beginning
5 of your statement, it will not preclude you from
6 speaking.

7 The FDA and this committee place great
8 importance in the open public hearing process. The
9 insights and comments provided can help the agency
10 and this committee in their consideration of the
11 issues before them. That said, in many instances
12 and for many topics, there will be a variety of
13 opinions. One of our goals today is for this open
14 public hearing to be conducted in a fair and open
15 way, where every participant is listened to
16 carefully and treated with dignity, courtesy, and
17 respect. Therefore, please speak only when
18 recognized by the chairperson. I appreciate your
19 cooperation.

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

1 record.

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

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

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

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

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

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

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

12 DR. HOFFMAN: Thank you.

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

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

1 no known conflicts of interest.

2 I'm here today -- my perspective's a little
3 different. I started out my career as an
4 epidemiologist. I was on the faculty at Yale and
5 Harvard, but then I came to Washington over
6 30 years ago, and I've really focused on health
7 policy issues since then.

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

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

1 memo regarding the data.

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

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

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

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

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

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

22 I'm very sympathetic, obviously, to patient

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

9 **Questions to the Committee and Discussion**

10 DR. HOFFMAN: Thank you.

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

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

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

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

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

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

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

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

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

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

1 I realize.

2 (Laughter.)

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

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

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

22 (No response.)

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

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

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

9 (Laughter.)

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

1 get their bladders out.

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

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

21 DR. HOFFMAN: Dr. Siddiqui?

22 DR. SIDDIQUI: Jumping in on this same

1 topic, I think that's a very meaningful question
2 that was asked, or thought that was posed, about
3 confusion about what happens to these patients,
4 because I think that it reflects the field right
5 now that affects urologists in general. I think
6 one thing that you can see is actually -- one of
7 the tables, it goes through what happened to these
8 patients after they were treated, and you'll notice
9 there's -- how many, 1, 2, 3, 4, 5, 6, 7,
10 8 -- 9 different types of intravesical therapies
11 ever given to this mixed population after they
12 failed to respond.

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

1 so that's a mess.

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

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

22 DR. HOFFMAN: Dr. Agarwal, you had a

1 comment?

2 DR. AGARWAL: Yes. Just to echo what my
3 colleagues have said here, I'm really conflicted.
4 I desperately want a therapy for bladder cancer
5 patients, but if that therapy is ultimately
6 resulting in half the patients getting a cystectomy
7 16 months, 13 months down the road, and in the
8 context of a trial where we didn't do random
9 biopsies and we didn't use blue light, which is
10 known to really pick up cases of CIS, are we really
11 looking at a 46 percent, 3-month complete response
12 or is it much lower than that?

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

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

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

11 DR. HOFFMAN: Dr. Uldrick?

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

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

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

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

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

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

22 DR. SIDDIQUI: I wanted to actually comment

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

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

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

1 percent of the time it has cancer. As far as I can
2 tell, the actual missed rate is probably closer to
3 5 percent, based on the literature I could find. I
4 found two studies, both said 5 percent, so as far
5 as I'm concerned, it's gold. But I think this is a
6 topic that's going to be hard to come up with the
7 concrete numbers, but that's the one thing that I
8 thought I would comment on there.

9 DR. HOFFMAN: Dr. Klepin?

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

1 10-year life expectancy, but we've moved them a
2 year or two down the road, and many of them are
3 still going to be moving towards surgery. At that
4 point, they may have some acquired comorbidities,
5 so are we then increasing some risk with their
6 ultimate surgical procedure? That was raised.

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

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

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

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

11 DR. HOFFMAN: Dr. Apolo?

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

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

22 DR. AGARWAL: I think what we probably would

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

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

19 DR. HOFFMAN: Dr. Cristofanilli?

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

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

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

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

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

4 DR. HOFFMAN: Dr. Hinrichs?

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

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

1 question.

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

13 DR. HOFFMAN: Dr. Murdock?

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

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

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

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

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

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

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

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

21 DR. HOFFMAN: Dr. Agarwal?

22 DR. AGARWAL: I think my one fear is

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

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

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

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

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

17 I don't think delays of whatever, 3 to
18 9 months, are going to be as helpful. And again,
19 in this very refractory, unresponsive
20 population -- and I said this before -- I am
21 concerned we're just letting the disease fester,
22 and get into the muscle, and make the cystectomy

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

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

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

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

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

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

18 (Dr. Klepin gestures no.)

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

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

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

15 Dr. Kraus?

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

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

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

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

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

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

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

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

15 DR. HOFFMAN: Dr. Agarwal?

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

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

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

19 DR. HOFFMAN: Dr. Murdock?

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

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

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

16 DR. HOFFMAN: Dr. Siddiqui?

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

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

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

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

1 DR. HOFFMAN: Dr. Hinrichs?

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

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

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

22 DR. HOFFMAN: Dr. Beaver?

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

7 DR. HOFFMAN: I think we should end the
8 discussion and proceed to the vote. We'll be using
9 an electronic voting system for this meeting. Once
10 we begin the vote, the buttons will start flashing
11 and will continue to flash even after you've
12 entered your vote. Please press the button firmly
13 that corresponds to your vote. If you're unsure of
14 your vote or you wish to change your vote, you may
15 press the corresponding button until the vote is
16 closed.

17 After everyone has completed their vote, the
18 vote will be locked in. The vote will then be
19 displayed on the screen, and the DFO will read the
20 vote from the screen into the record. Next, we'll
21 go around the room and each individual who voted
22 will state their name and vote into the record.

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

3 (Voting.)

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

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

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

18 Dr. Apolo?

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

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

3 DR. HOFFMAN: Dr. Klepin?

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

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

22 It would be nice to have, if this is

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

8 DR. HOFFMAN: Dr. Hinrichs?

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

20 DR. HOFFMAN: Dr. Halabi?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 But I feel like our field does do that, that

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

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

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

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

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

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

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

22 What we're being asked here by Dr. Suzman

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

8 Am I saying that right?

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

11 DR. HOFFMAN: Oh, yes.

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

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

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

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

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

22 I welcome other comments.

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

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

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

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

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

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

15 DR. HOFFMAN: Any dissenting votes?

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

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

1 eliminate any quality-of-life data.

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

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

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

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

12 DR. HOFFMAN: Ms. Johnston?

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

17 **Adjournment**

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

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

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

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