FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Virtual Meeting

Thursday, February 9, 2023

11:00 a.m. to 5:22 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Rhea Bhatt

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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(Chairperson)

Chief, Division of Solid Tumor Oncology

George and Edith Richman Distinguished Scientist

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Professor of Medicine and Urology

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University Hospitals Seidman Cancer Center

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Herbert Irving Comprehensive Cancer Center

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(Non-Voting)

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(11:00 a.m.)

Call to Order

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

My name is Jorge Garcia, and I will be chairing today's meeting. I will now call the first session of the February 9, 2023 meeting of the Oncologic Drug Advisory Committee to order. Rhea Bhatt is the acting designated federal officer for this meeting, and she will begin with introductions.

Introduction of Committee

MS. BHATT: Good morning. My name is Rhea Bhatt, and I'm the acting designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation. We'll begin with the ODAC members, starting with Dr. Conaway.

(No response.)

MS. BHATT: Dr. Conaway, would you be able to unmute yourself and introduce yourself to the committee?

DR. CONAWAY: Mark Conaway, University of Virginia.

MS. BHATT: Thank you, Dr. Conaway.

Next, we have Dr. Garcia.

DR. GARCIA: Jorge Garcia. I'm a GU medical oncologist, a professor of medicine and urology, and the chair of solid tumor oncology at University Hospitals Seidman Cancer Center at Case Western Reserve University in Cleveland, Ohio.

MS. BHATT: Thank you.

Next, we have Dr. Kunz.

DR. KUNZ: Hi. Good morning. My name is Pamela Kunz, and I'm an associate professor of medicine and medical oncology at Yale Cancer Center and Yale School of Medicine, where I serve as the division chief for GI Medical Oncology. Thank you.

MS. BHATT: Thank you, Dr. Kunz.

Next, we have Dr. Lieu.

DR. LIEU: Hi, everybody. My name is Chris Lieu. I'm a GI medical oncologist and associate professor of medicine at the University of Colorado Cancer Center. I also serve as the associate director for clinical research.

MS. BHATT: Thank you.

Dr. Madan?

DR. MADAN: Good morning. My name is Ravi Madan. I'm a medical oncologist at the National Cancer Institute. I'm head of the prostate cancer clinical research section here at the NCI. Thank you.

MS. BHATT: Thank you, Dr. Madan.

Next, we have our consumer representative, Mr. Mitchell.

MR. MITCHELL: I'm David Mitchell. I am the president of an organization called Patients for Affordable Drugs, and I'm a multiple myeloma patient.

MS. BHATT: Thank you, Mr. Mitchell.

Next, Dr. Nieva.

DR. NIEVA: Hi. I am Jorge Nieva, a

thoracic medical oncologist, section head of solid tumors, University of Southern California Norris Comprehensive Cancer in Los Angeles, California.

MS. BHATT: Thank you, Dr. Nieva.

Dr. Vasan?

DR. VASAN: Hi. My name is Neil Vasan. I'm a breast medical oncologist and assistant professor at Columbia University, Irving Cancer Center, and I'm also a laboratory head and a laboratory-based physician scientist.

MS. BHATT: Thank you, Dr. Vasan.

Next, we will move on to temporary voting members. First, we have Dr. Chang.

DR. CHANG: Good morning. My name is George Chang. I'm a professor and chair ad interim in the Department of Colon and Rectal Surgery at the University of Texas, MD Anderson Cancer Center. Thank you.

MS. BHATT: Thank you.

Next, we have Dr. Ciombor.

DR. CIOMBOR: Hi. I'm Kristen Ciombor. I'm a GI medical oncologist and associate professor of

medicine at Vanderbilt University.

MS. BHATT: Thank you.

Dr. Katsoulakis?

DR. KATSOULAKIS: Hi. I'm Evangelia Katsoulakis. I'm a radiation oncologist and clinical informaticist. I work for the James Haley Tampa VA in [indiscernible] informatics, and associate professor of radiation oncology at the University of South Florida School of Medicine and Tampa General Hospital. Thank you.

MS. BHATT: Thank you.

Next, we have our patient representative, Mr. Majkowski.

MR. MAJKOWSKI: Good morning. I'm Paul Majkowski, patient representative, a rectal cancer survivor from Albertson, New York.

MS. BHATT: Thank you, Mr. Majkowski.

Dr. Park?

DR. PARK: Hi. John Park, radiation oncologist at the Kansas City VA. I'm also the co-chair of the pharmacy and therapeutic community here; glad to be here today.

MS. BHATT: Thank you, Dr. Park.

Next, we have our industry representative, Dr. Kraus.

DR. KRAUS: Hi. Good morning, everyone. Albert Kraus, industry representative. I'm a biologist with decades of drug development, cancer drug development in particular experience, and I'm currently an employee of Pfizer.

MS. BHATT: Thank you, Dr. Kraus.

Next, we'll move on to FDA participants.

First, we have Dr. Pazdur.

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

MS. BHATT: Thank you.

Next, Dr. Kluetz.

DR. KLUETZ: Hi. My name is Paul Kluetz. I'm the deputy director for the Oncology Center of Excellence at the FDA.

MS. BHATT: Thank you.

Dr. Lemery?

DR. LEMERY: Hello. Steven Lemery,

director, DO3.

MS. BHATT: Thank you.

Dr. Fashoyin-Aje?

DR. FASHOYIN-AJE: Lola Fashoyin-Aje, deputy director, Division of Oncology 3.

MS. BHATT: And Dr. Casak?

DR. CASAK: Good morning. I'm the acting team leader for the gastrointestinal and malignancies team in the Division of Oncology 3.

MS. BHATT: Thank you. That concludes panel and FDA introductions.

Dr. Garcia?

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

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

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

Rhea Bhatt will now read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

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

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

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

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

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

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

Today's agenda involves the discussion of the investigational new drug application 157775, for dostarlimab-gxly for injection, submitted by GlaxoSmithKline. The proposed indication, or use, for this product is as a single agent for the treatment-naïve mismatch repair deficiency/ microsatellite instability-high rectal cancer. FDA would like to obtain the committee's input on the following: 1) the adequacy of proposed trials to

evaluate the benefits and risks of dostarlimab for the proposed indication, including trial design, study population, clinical endpoint, and patient follow-up; and 2) the adequacy of the proposed data package to permit an assessment of the benefits and risks of dostarlimab for the proposed indication.

This is a particular matters meeting during which specific matters related to GlaxoSmithKline's IND will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. Kristen Ciombor.

Dr. Ciombor's waiver involves her employer's research funded by the National Cancer Institute for which her employer received between $0 and $8,000 per patient enrolled in the research study. The waiver allows this individual to participate fully in today's deliberation. FDA's reasons for issuing the waiver are described in the waiver documents, which are posted on FDA's website at

fda.gov/advisorycommittees/committeesandmeetingmaterials/humandrugadvisorycommittees. Copies of the waiver may also be obtained by submitting a written request to the agency's Freedom of Information Division, 5630 Fishers Lane, Room 1035, Rockville, Maryland, or requests may be sent via fax to 301-827-9267.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Albert Kraus is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Kraus' role at this meeting is to represent industry in general and not any particular company. Dr. Kraus is employed by Pfizer.

For the record, Dr. Kimmie Ng has acknowledged being a principal investigator or co-investigator for several contracts or grants

involving the National Cancer Institute; Cancer Research UK; Colorectal Cancer Alliance; Pharmavite; Evergrande Group; Janssen; and Revolution Medicines.

Dr. Ng has acknowledged receiving speaker fees from Bayer and being the scientific advisor for Pfizer and Bayer. Dr. Ng has acknowledged being the scientific advisor for GlaxoSmithKline and receiving less than $10,000 in 2022. As a guest speaker, Dr. Ng will not participate in committee deliberations, nor will Dr. Ng vote.

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

Back to you, Dr. Garcia.

DR. GARCIA: Thank you, Ms. Bhatt.

We will now proceed with the FDA introductory comments from Dr. Lola Fashoyin-Aje.

FDA Opening Remarks - Lola Fashoyin-Aje

DR. FASHOYIN-AJE: Good morning, members of the committee, the GlaxoSmithKline team, invited guests, and FDA colleagues. I'm Lola Fashoyin-Aje, and I'm a medical oncologist and the deputy director for the Division of Oncology 3. I welcome you all to this convening of the Oncologic Drugs Advisory Committee to discuss the proposed clinical development program for dostarlimab, for the treatment of deficient mismatch repair or microsatellite instability-high locally advanced rectal cancer.

Dostarlimab is an approved programmed death receptor-1-blocking monoclonal antibody. GlaxoSmithKline, heretofore referred to as GSK, is developing dostarlimab for the treatment of patients with deficient mismatch repair or microsatellite-high locally advanced rectal cancer,

which I will refer to as the proposed indication throughout my presentation. Prior to providing you an overview of the issues for discussion today, I refer the committee to reports of the preliminary efficacy results of a single institution study of dostarlimab in patients with deficient mismatch repair, locally advanced rectal cancer. These results have been discussed at major oncology conferences and have been reported on in prominent journals.

In this single-arm study conducted at the Memorial Sloan Kettering Cancer Center, patients received dostarlimab every 3 weeks for 6 months, followed by non-operative care and were followed for clinical response. In a report published in the New England Journal of Medicine, study investigators reported a 100 percent clinical complete response rate for all 12 participants who had completed treatment. After a median follow-up of one year, none had needed other treatments or had had cancer regrowth.

These results have generated enthusiasm and

caution in equal measure. If demonstrated to be safe and efficacious in clinical trials, treatment with dostarlimab will likely change the treatment paradigm for this disease, providing a radiation-free, non-operative management treatment option for patients with locally advanced rectal cancer who would typically receive multimodality therapy that is associated with substantial toxicity and lifelong treatment-related sequelae. However, the preliminary nature of these data cannot be overstated, and further study is needed to determine whether these results can be replicated in a larger cohort of patients and across many different clinical care settings that have variable expertise in the non-operative management of this disease.

My presentation will follow this outline. I will conclude my remarks by presenting the topics for which FDA is seeking the committee's thoughtful discussion and recommendation.

We referred this program for discussion at the ODAC, as we have typically done, to ensure

transparency and to get input from the community on the clinical and regulatory issues before the FDA. GSK proposes to conduct a multicenter, single-arm trial similar to the previously described single institution study. The two trials will evaluate dostarlimab as a treatment that would replace the current standard of care, which is administered with curative intent.

The primary efficacy endpoint is clinical complete response at 12 months. Data from these two single-arm studies are proposed to be the basis of a marketing application seeking accelerated approval. Analysis of clinical complete response and event-free survival, after additional follow-up, are proposed to provide confirmatory evidence of dostarlimab's effectiveness.

We are asking the committee to discuss and provide input on the adequacy of the proposed strategy to demonstrate the safety and effectiveness of dostarlimab as a treatment for dMMR/MSI-high locally advanced rectal cancer. We would like your thoughtful input on the measures

that can be taken now, early in the clinical development of dostarlimab, to generate the data that will demonstrate the safety and effectiveness of dostarlimab for the proposed indication, specifically with respect to the proposed use of single -arm trials in the curative-intent setting; the clinical endpoints; the patient population; and the adequacy of the data to be generalizable to patients with locally advanced rectal cancer and across diverse treatment settings with respect to experience administering non-operative management.

I will now provide a brief overview of the disease background. Please note that FDA's invited guest from the Dana-Farber Cancer Institute will provide a more extensive review of rectal cancer treatment and outcomes using standard-of-care treatment, as well as the non-operative management approach that is used at some highly specialized centers.

Rectal cancer is often described together with colon cancer, which may result in underestimation of its true incidence. According

to the American Cancer Society, an estimated 46,000 cases will be diagnosed this year in the United States. Approximately 12 to 15 percent of colorectal cancer cases are dMMR/MSI-high, with decreasing frequency as stage of the disease increases from stage I to stage IV. The data for dMMR prevalence in rectal cancer are limited, but published reports indicate 2 to 20 percent of rectal cancers are dMMR. Treatment of rectal cancer varies by stage, and treatment of stage II and III disease is the topic for discussion today.

This slide depicts the standard-of-care treatment of locally advanced rectal cancer and outcomes, and please note that this treatment paradigm is applied irrespective of MMR or MSI status. Details regarding the preferred neoadjuvant chemotherapy and radiotherapy regimens and treatment sequencing used will be discussed in subsequent presentations, but following completion of neoadjuvant treatment, patients undergo resection of the rectum and may receive additional chemotherapy postoperatively. While outcomes are

generally good, some patients do experience local tumor returns and distant tumor metastases. Treatment-related adverse events can be significant.

As a result, interest in a surgery-sparing or non-operative management approach has been the subject of ongoing investigation. This approach requires careful monitoring or watchful waiting of patients who have a clinical response to chemoradiation or chemoradiation plus chemotherapy; however, use of a non-operative management strategy is variably implemented, largely based on institutional experience and expertise, and due to the limitations of the historical data that informs current use of this approach.

Variability exists with respect to patient selection, treatment administered prior to the period of watchful waiting, and in the clinical assessment methods used to determine clinical response. This slide illustrates the market heterogeneity across studies with variability at practically every decision point in the continuum

of this approach, as highlighted by the orange arrows.

The differences across studies pose challenges for establishing benchmarks for the non-operative management approach. Shown here are the largest series describing outcomes in patients who underwent non-operative management. These studies will be reviewed in detail in subsequent presentations.

The only prospective evaluation of the non-operative management approach to date is shown on the right column. The organ preservation of rectal adenocarcinoma, or OPRA trial, investigated non-operative management using different sequencing of chemotherapy and chemoradiotherapy in patients with locally advanced rectal cancer. Patients were randomized to one of two treatment arms of 5FU and oxaliplatin-based chemotherapy, followed by chemoradiation or the reverse. Please note the differences in tumor regrowth and organ preservation rates across arms, which differed only in the sequencing of therapy.

To summarize, there is market heterogeneity across studies evaluating patients who underwent non-operative management for locally advanced rectal cancer, leading to residual uncertainties that stem from challenges in interpreting results. Consequently, benchmarks for the non-operative management approach have not been established in the overall locally advanced rectal cancer population, let alone in the dMMR/MSI-high population.

Relevant to today's discussion is the unclear relationship of clinical complete response to long-term outcomes of benefit, and equally as important is the unclear significance of clinical complete response observed in the setting of chemotherapy and radiation therapy versus a clinical complete response in the setting of a radiation-free treatment approach as proposed in the dostarlimab program.

I will now very briefly describe the dostarlimab development program, as the applicant will be discussing this in greater detail. I will

highlight some regulatory considerations. Although we will not be discussing the benefit-risk assessment in the context of a marketing application, I will briefly review FDA's evidentiary standard for approval because we are asking the committee to provide input on the adequacy of the proposed data package, which GSK intends to be the basis of a BLA submission. To receive approval, a sponsor must provide evidence that the drug is safe and effective for its intended use, and the data must come from adequate and well-controlled trials.

There are two approval pathways. Accelerated approval is granted to drugs that treat serious or life-threatening diseases to address an unmet medical need, and approval is granted based on an improvement over available therapy as measured by an intermediate endpoint that can be evaluated earlier before irreversible morbidity or mortality, and that is reasonably likely to predict clinical benefit.

In granting accelerated approval, FDA may

require confirmatory trials to verify and describe clinical benefit, and traditional approval is generally granted to drugs that demonstrate clinical benefit as measured by effects on how patients feel, function, or survive.

For approvals in the early non-metastatic, curative-intent setting, FDA has typically requested randomized-controlled trials that compare an investigational therapy to standard of care or that evaluate the investigational agent as an add-on to standard of care with approval based on established endpoints of clinical benefits such as survival.

Regulatory dossiers that include analysis of time-to-event endpoints in the context of a single-arm trial are discouraged because the results are uninterpretable in the absence of a comparator group. A noteworthy exception to these general principles is the use of a durable complete response rate as an endpoint in single-arm trials investigating therapies for patients with BCG unresponsive, high-risk, non-muscle invasive

bladder cancer with carcinoma in situ. In this clinical scenario, cystectomy provides a curative option, but it is associated with significant morbidity and a 90-day mortality rate that may be as high as 10 to 15 percent in older patients.

The considerations for acceptance of a complete response rate evaluated in a single-arm trial in this curative setting to support approval of products for the treatment of BCG unresponsive, high-risk, non-muscle invasive bladder cancer in situ include the lack of suitable therapy to serve as comparator in randomized clinical trials and public stakeholder discussions with FDA's participation and agreement on endpoints, trial designs, treatment assessment and follow-up that would be adequate for trials designed to support regulatory action, and FDA subsequent guidance to industry that describes FDA's expectations for an adequate data package.

The top of this slide shows the two single-arm studies that GSK plans to submit in a future marketing application. The key efficacy

endpoints are shown in the right column. Clinical complete response rate at 12 months is proposed to support an application for accelerated approval, and in blue are the endpoints proposed to confirm and verify clinical benefit. A third study of perioperative dostarlimab in locally advanced colon cancer is proposed to provide supportive evidence of the safety and effectiveness of dostarlimab.

I will now present the discussion topics. To facilitate adequate discussion across select issues regarding GSK's program, we have identified topics for discussion. While these are related issues, we ask that the committee allot time to discuss each topic separately to facilitate clear understanding of the committee's perspective and recommendations.

As a first topic, please discuss the adequacy of the proposed single-arm trials to evaluate the efficacy and safety of dostarlimab, including the long-term benefits and risks of treatment, taking into account the curative-intent setting and the fact that available non-operative

management treatment option includes radiotherapy.

We are also seeking the committee's input on the adequacy of the proposed clinical endpoints to characterize and verify the benefit of dostarlimab. Please take into account the uncertainties regarding the relationship between clinical complete response rate and endpoints denoting clinical benefit in the context of current treatment options. Discuss the magnitude and durability of clinical complete response rates that is reasonably likely to predict clinical benefit and the adequacy of event-free survival investigated in a single-arm trial to characterize clinical benefit.

As a third topic, discuss relevant issues to be considered in the general locally advanced rectal cancer population, which represents a heterogeneous group with respect to risk of recurrence, and the potential impact of a non-operative management approach that importantly will not include radiation therapy for local control.

Are there subgroups within the locally advanced rectal cancer entity for whom the benefit-risk assessment would differ significantly using a non-operative approach; that is for whom surgical resection is necessary to achieve long-term outcomes? Are there patients who are at higher risk of recurrence, who should be adequately represented in the proposed clinical studies to inform the benefits and risks of dostarlimab across the population?

Finally, discuss the potential impact of the variability in care, expertise, and experience across diverse clinical settings on study conduct, and ultimately on outcome. Should site selection for the proposed trials consider the diverse settings that will likely administer dostarlimab should it be approved?

Following what we hope will be an informative discussion, we ask that the committee vote on the following question. Will the data from the proposed single-arm trials, enrolling a total of 130 patients, be sufficient to characterize the

benefits and risks of dostarlimab in the curative-intent setting that is dMMR/MSI-high, locally advanced rectal cancer?

This concludes my presentation. I thank you for your attention.

DR. GARCIA: Thank you, Dr. Fashoyin-Aje.

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

For this reason, FDA encourages all applicants, including the GlaxoSmithKline, LLC non-employee presenters, to advise the committee of any financial relationship they may have with the sponsor, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based on the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the

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

We will now proceed with the presentations from GlaxoSmithKline.

Applicant Presentation - Ivan Diaz-Padilla

DR. DIAZ-PADILLA: Good morning. My name is Ivan Diaz-Padilla, and I'm responsible for immuno-oncology clinical development at GSK. We look forward to today's discussion about our planned study, which has been designed to objectively evaluate the benefit-risk of dostarlimab for treatment-naïve rectal cancer patients. This is a study that, if successful, is likely to change the treatment paradigm.

First, it is important to note that mismatch repair deficient microsatellite instability-high tumors, known as dMMR/MSI-high, are highly susceptible to checkpoint inhibitors. This is due to several factors, including increased expression

of PD-1 and PD-L1 in tumors, increased tumor infiltrated lymphocytes, and increased neoantigen due to high tumor mutational burden.

A subset of rectal cancer is caused by this rare mutation. Like in other solid tumors, dMMR/MSI-high has become a well-established predictive biomarker of response to PD-1 inhibition, and that is also the case in rectal cancer. As such, NCCN guidelines recommend its testing for all patients with rectal cancer.

Dostarlimab is an established anti-PD-1 monoclonal antibody for advanced, recurrent dMMR/MSI-high tumors. It has received accelerated approval in two indications for adult patients: first, for endometrial cancer that has progressed on or following treatment with a platinum-containing regimen; and second, for any solid tumor that has progressed on or following treatment, and for which there is no alternative treatment option.

These indications are based on our GARNET multicohort, single-arm trial, where dostarlimab

demonstrated deep and durable responses in second-line and beyond dMMR/MSI-high solid tumors. GARNET showed an objective response rate of 44 percent. The median duration of response was not reached, and the estimated percent of patients maintaining a response for 12 and 24 months was 92 percent and 85 percent, respectively.

Importantly, for our discussion today, the study included 105 patients with colorectal cancer and demonstrated a confirmed objective response rate of 43 percent. While the median duration of response was not reached, it ranged from to 2.8 to 41.5 months. Understanding dostarlimab's effectiveness in metastatic dMMR/MSI-high it was also hypothesized that it could also be affected in locally advanced cancers.

To investigate this, a team of researchers at the Memorial Sloan Kettering Cancer Center is running an ongoing study using dostarlimab monotherapy earlier in a patient's rectal cancer treatment journey [indiscernible]. As you will hear, this study is evaluating neoadjuvant

dostarlimab in dMMR/MSI-high locally advanced rectal cancer and has demonstrated unprecedented efficacy, delivering clinical complete responses in all patients.

For those patients eligible for a 12-month evaluation following treatment with dostarlimab, the response has persisted. All have sustained their complete clinical response, achieving a cCR 12; and further, all patients have avoided the adverse effect associated with the standard of care.

Following these results, GSK designed a larger global study with endpoints that align with the MSK study to further demonstrate the benefit of dostarlimab in these patients. The study intends to enhance the robustness and demonstrate reproducibility of the MSK methods. This is the study design being presented for your input today. It is also the study we plan to pool with the results from MSK to support accelerated approval in this indication.

Study 219369 is a multicenter, single-arm,

phase 2 study that will establish the efficacy of dostarlimab in locally advanced dMMR/MSI-high rectal cancer. The primary endpoint is a sustained clinical complete response for 12 months, cCR12. Published evidence shows that achieving a cCR12 predicts long-term clinical benefit, including being potentially curative without the need to surgically remove the rectum, which often happens with the current standard of care. We plan to start enrolling patients in April of this year.

Let me take a moment to define clinical complete response and cCR12. First, it is important to understand that a clinical complete response is a stringent endpoint defined as the absence of any abnormality or residual disease based on both endoscopic and MRI examinations. Assessing cCR following the adjuvant treatment is being pursued by investigators as a means to manage a patient's cancer with a non-operative approach, with the goal of organ preservation.

cCR12 builds on the stringency upon initial cCR to demonstrate durability 12 months following

completion of therapy. During this time, patients are carefully monitored with a non-operative management approach. Sustaining a clinical complete response for 12 months predicts disease-free survival at 5 years, another long-term clinical benefit, including overall survival.

With that as an introduction, here's the agenda for the rest of our presentation. All external presenters have been compensated for their time to prepare for this meeting, and now I will turn it over to Dr. Cercek.

Applicant Presentation - Andrea Cercek

DR. CERCEK: Thank you, Dr. Diaz-Padilla.

Good morning. I'm Andrea Cercek from Memorial Sloan Kettering. I'm glad to have the opportunity to discuss the challenges we face in caring for our patients with dMMR/MSI-high locally advanced rectal cancer.

To begin, it's important to understand that we are discussing a rare form of a serious cancer. Locally advanced rectal cancer is defined as either stage II or III disease, and in the United States,

more than 20,000 individuals are diagnosed with this stage of rectal cancer every year; and of, those, only about 5 to 10 percent are known to have the dMMR/MSI-high mutation, which is a distinct group within the overall rectal cancer population. Biomarker status varies across rectal tumor stages. The highest incidence occurs in stage II, and then decreases with increasing stage.

So let's review the current treatment approaches. There are two established standards of care for treating dMMR/MSI-high locally advanced rectal cancer. Both include trimodality therapy with chemotherapy, radiation, and surgery, which is also known as total mesorectal excision where the rectum is removed.

One approach, standard neoadjuvant therapy, utilizes neoadjuvant chemoradiation, followed by surgery, and then adjuvant chemotherapy. The second approach is known as total neoadjuvant therapy, or TNT, where all treatment is given up front before surgery. And while these intense standards of care can be curative, approximately

one-third of patients still succumb to metastatic disease.

Many patients undergoing a total mesorectal excision require a temporary colostomy, and up to 30 percent become permanent due to the tumor location. Colostomies are associated with a variety of issues, including social/physiological dysfunction, depression, and stoma complications. Even without a permanent colostomy, the effects of surgery and radiation may impair survivorship and a patient's quality of life.

Following a partial or total resection of the rectum, patients can experience low anterior resection syndrome, which is manifested by fecal incontinence, urgency, and diarrhea. In addition, rectal surgery results in sexual dysfunction in the majority of patients and can also lead to urinary dysfunction. Finally, radiotherapy results in infertility and menopause in women due to the location of the ovaries and uterus within the radiation field, and has also been associated with a 3-fold increased risk of developing gynecologic

cancers.

These serious complications are among the reasons why there has been a growing movement towards non-operative management to achieve a clinical complete response after neoadjuvant therapy. In fact, NCCN guidelines state that a non-operative approach may be undertaken in centers with multidisciplinary teams that can objectively determine a cCR. So not only do we have stringent criteria to determine a clinical complete response, but the protocol for non-operative management is also rigorous and includes careful monitoring throughout a 5-year surveillance period. This enables early detection of any tumor regrowth, allowing for timely treatment.

Despite these advances that have improved the rates of complete responses, the majority of patients are not candidates for non-operative management and are therefore unable to avoid surgery and its associated functional compromise; and this is within a population of all locally advanced rectal cancer patients.

Data have shown that the tumors that are dMMR/MSI-high are less sensitive to chemotherapy. These outcomes emphasize the high unmet need for patients with this rare form of rectal cancer. They are treated with a standard of care that may be curative but also carries significant morbidities and long-term sequelae. As such, our research at Memorial Sloan Kettering is not only focusing on identifying a more efficacious treatment for this biomarker-selected population, but also one that offers reduced morbidities and the potential for organ preservation with non-operative management.

Let me now introduce my colleague, Dr. Josh Smith, who will walk you through the scientific rationale underpinning the selection of a sustained clinical complete response as a primary endpoint.

Applicant Presentation - Joshua Smith

DR. SMITH: Thank you, Dr. Cercek.

I'm Josh Smith, surgical oncologist and associate attending surgeon from Memorial Sloan Kettering Cancer Center. Let's start with how a

clinical complete response is correlated with disease-free survival at 3 years in a neoadjuvant chemoradiation setting.

These data from the landmark organ preservation in rectal adenocarcinoma trial, or OPRA, were presented at ASCO in 2021. OPRA was the first prospective trial investigating non-operative management in locally advanced rectal cancer patients who achieved cCR after total neoadjuvant therapy. As seen in yellow, patients who attained a clinical complete response, which excludes near complete response, were more likely to be alive at 3 years without disease, keep their organs, and avoid surgery for 3 consecutive years compared to patients with a near or incomplete response.

Here's a map showing the multiple institutions across North America that were all contributors in the OPRA trial. These sites were geographically diverse and included both academic and non-academic centers. When I reflect on OPRA, I see two key ingredients to its success. First, we were able to create consensus criteria that

standardize the evaluation and determination for cCR using input from global experts; and second, we were able to then implement these criteria prospectively to allow for non-operative management in patients who achieve a clinical complete response. These are critically important considerations since the potential for inter-site variability was one of the questions FDA has raised.

Now, let's consider patient outcomes based on achieving a cCR12. Here, I'm presenting published data showing that achieving a sustained cCR for 12 months is predictive of long-term clinical outcomes. When looking at disease-free survival on the top plot and overall survival on the bottom, 92 percent of patients achieved a cCR and were managed by watch and wait, and had 5-year disease-free survival, and 100 percent achieved 5-year overall survival. As you can see, the results are for patients achieving a cCR12 or higher compared to those who achieved a pathologic complete response after neoadjuvant chemoradiation,

compared with radical surgery for both 5 years disease-free and overall survival.

Now focusing on anti-PD-1 efficacy in dMMR/MSI-high colorectal tumors, here are published data from phase 2 and retrospective studies that consistently demonstrate high complete response rates when anti-PD-1s are used as neoadjuvant therapy. These dMMR/MSI-high tumors showed consistent susceptibility to immunotherapy, providing confidence in the ability to attain high rates of complete response.

It's also critical to mention the growing consensus in the patient and medical communities for adopting the non-operative management approach and cCR as an endpoint in rectal cancer clinical trials. Data from the OPRA trial, as well as in the retrospective analyses I just reviewed have resulted in patients expressing unwillingness to be randomized to radical surgery versus the non-operative management approach after achieving a cCR to neoadjuvant treatment.

Data are also influencing the medical and

research community, and here I'm showing three new large prospective studies in rectal cancer that have adopted non-operative management in cCR as an endpoint. The first is the National Cancer Institute sponsored JANUS rectal cancer trial. I'm the primary investigator, and we plan to enroll more than 300 participants with locally advanced rectal cancer; and I'll note that we are excluding patients with dMMR tumors since we believe they're a different population and may not be sensitive to chemotherapy.

The Japanese study that was just presented at the ASCO GI symposium last month, and importantly also excludes dMMR/MSI-high rectal cancer patients, is important to note. Notably, the 700-patient German study has rapidly accrued more than 50 percent of the patients given the integrated non-operative management approach cCR endpoint and of course patient interest.

One final point is that in the event that a patient does experience a local regrowth of their primary tumor, data support our ability to

successfully perform surgery and deliver favorable outcomes. In OPRA, disease-free survival rates were similar for patients who had TME at restaging versus those who had TME at regrowth. The operation we perform in this situation is exactly the same we would have offered the patient after total neoadjuvant therapy completion, and data and experience supports that their long-term clinical outcomes, including disease-free survival, would not be compromised. Our MSK experience and other series support these findings.

I'll turn now the presentation back to Dr. Cercek to describe the design and interim results from our MSK study.

Applicant Presentation - Andrea Cercek

DR. CERCEK: Thanks, Dr. Smith.

The hypothesis of our study at MSK is that we could use neoadjuvant dostarlimab to either replace chemotherapy, or replace chemotherapy and radiation, or to replace all three components of the current standard of care -- chemotherapy, radiation, and surgery -- and I'll start with the

design.

This is an ongoing open-label, single-arm, prospective phase 2 study of dostarlimab in patients with treatment-naïve locally advanced dMMR/MSI-high rectal cancer. Our initial target enrollment was 30 patients. Eligible patients with stage II or III disease received 500 milligrams of dostarlimab every 3 weeks for 6 months. Patients have 2 assessments during dostarlimab treatment, and after 6 months of treatment, they are evaluated for response with imaging and endoscopy.

Patients who achieve a clinical complete response at that time have the opportunity to proceed to non-operative management with active surveillance. Sustaining their clinical complete response for 12 months means they have achieved a cCR12. Patients who do not achieve a clinical complete response after 6 months of dostarlimab go on to receive standard-of-care chemoradiation followed by another assessment of tumor response. The patients who at that time achieve a clinical complete response have the opportunity to proceed

with non-operative management, however, if there's residual disease at that time, then they receive standard-of-care surgery.

Our study is using two co-primary endpoints. The first is ORR, defined as complete response, near complete response, or partial response; and the second is cCR12, defined as sustained clinical complete response for 12 months after completion of dostarlimab, which is evaluated at 18 months since the start of treatment and determined by a multidisciplinary team or a pathologic complete response in patients who require surgery.

Patients obtaining a clinical complete response would continue with non-operative management that includes intense monitoring to confirm continued cCR at each evaluation. To that end, we're performing assessments every 4 months for 2 years, and then every 6 months in years 3 through 5, which is more frequent than standard-of-care practice. The assessments include imaging, endoscopic exams, biopsies, as well as blood tests; and I'll note here that are

non-operative management approach is similar to the surveillance used in the prospective OPRA trial.

Here you can see the study demographics at the time of our most recent public presentation at ASCO in June of 2022, where we reported on the first 18 patients in the study. We are enrolling the population that is representative of locally advanced dMMR/MSI-high rectal cancer. I'll note that the majority of tumors were large, bulky tumors; 78 percent of them were T3 and T4; 94 percent were node positive, which means that these patients would almost certainly have required all three components of standard-of-care treatment.

Now moving on to the results, all patients, 100 percent of them, achieved a clinical complete response following 6 months of dostarlimab. No patient required chemoradiation, chemotherapy, or surgery; and thus far, in terms of risk for treatment, all adverse events were grade 1 or 2 and the safety profile is in line with other checkpoint inhibitors.

On this slide, I'm presenting the baseline

and then serial imaging for just one of our patients who achieved a cCR. This is a young woman who was 30 years old at the time when she presented after having several months of symptoms. At the very top-left picture is their initial endoscopic exam. You can clearly see a large nearly obstructing tumor. The tumor is visible on the MRI as depicted by the red arrow, and this was graded as a T3 node-positive tumor.

She had her first endoscopic evaluation at 6 weeks, and this is after just 2 doses of dostarlimab. You can clearly see that the tumor has decreased significantly. This was assessed as a partial response. There's still some residual disease, but her symptoms had already improved. At 3 months, while the endoscopic exam appeared normal and indicated a cCR, the MRI showed a bit of residual tumor, so she was graded as a near CR, and at 6 months, after completion of all planned dostarlimab therapy, she achieved a cCR by endoscopy and MRI, and moved into the non-operative management phase of the study. She maintained her

cCR for 12 months after therapy, achieving a cCR12, which is indicated here as an 18-month follow-up assessment. She now has had 28 months of follow-up and remains disease-free. Importantly, she feels great and has no lingering effects from treatment.

Now I'll go on to the full patient population and the long-term follow-up. Here we're showing the updated data from the initial 18 patients that were presented in June of 2022 at ASCO, so this was from 8 months ago, now updated. Patients have completed 6 months of dostarlimab treatment, and all patients consecutively have achieved and maintained a clinical complete response, as noted by the yellow dot and green bar. Thus, our complete response rate remains at 100 percent.

The first 10 patients have achieved 18 months of follow-up post dostarlimab and remain in clinical CR, achieving a cCR12; 4 patients have reached 30 months of follow-up, achieving a cCR24; and further, no patient has experienced disease progression or a recurrence, with a median

follow-up of 18.3 months.

Since the presentation in June, we've enrolled a total of 30 patients. To date, we continue to see enduring responses in all treated patients, and every patient who completed 6 months of dostarlimab has achieved a clinical complete response. We anticipate presenting updated data, including long-term follow-up in the second quarter of 2023.

Our study at MSK is showing that dMMR/MSI-high locally advanced rectal cancer is highly sensitive to neoadjuvant monotherapy with dostarlimab, and while the short-term benefits appear significant, we need long-term data with additional patients to demonstrate the durability of results and to better understand our ability to successfully retreat in the event that the cancer reappears. This underscores the importance of the proposed GSK study. A positive study will confirm the unprecedented efficacy we have seen with dostarlimab; it will allow us to eliminate tumors as demonstrated by a cCR; and it will also collect

data to confirm that cCR12 predicts for long-term benefit. And with that, I'll turn the presentation over to Dr. Diaz-Padilla.

Applicant Presentation - Ivan Diaz-Padilla

DR. DIAZ-PADILLA: Thank you, Dr. Cercek.

I will now discuss the design of Study 219369, which has been designed to confirm the results of the MSK study in a larger global population and demonstrate reproducibility. Importantly, this case study design reflects input for more than 30 global key opinion leaders who have specialized in rectal cancer. Treatment-naïve patients with dMMR/MSI-high locally advanced rectal cancer would receive dostarlimab 500 milligrams every 3 weeks for 9 cycles. At that time, patients will undergo post-intervention assessment based on endoscopy, rectal, MRI, and CT scan of the chest, abdomen, and pelvis.

Patients meeting the criteria for complete clinical response will begin non-operative management along with rigorous monitoring and assessment that will be more extensive than

surveillance for patients who undergo surgery. Evaluations include MRIs, CT scans, and endoscopies every 4 months for the first 2 years, and then twice a year through year 5. In the event of residual disease or recurrence, patients will be managed with local standard of care.

To address the appropriateness of a single-arm study, it is critical to keep in mind the imbalance in both the frequency and nature of toxicities between dostarlimab and the standard of care. With the known treatment associated morbidities of radiation and surgery, we would anticipate high rates of drop outs in a control arm.

Second, the efficacy of dostarlimab in these dMMR populations is well known, with a 100 percent clinical complete response rate from the Cercek [indiscernible] study. As such, patients and physicians may be reluctant to participate in a study where patients could be randomized to standard of care. And lastly, I will also note that we are only enrolling patients with dMMR/MSI-

high rectal cancer, a rare tumor with a limited number of histologically confirmed patients.

We plan to recruit patients who are representative of the global patient population. Our enrollment criteria will mirror those of the MSK study. We anticipate broad global participation of more than 45 sites with multidisciplinary teams that will adapt a regression schema for evaluating tumors similar to the OPRA trial. Centers will be in the U.S., Europe, and the rest of the world.

Here are the study's prespecified primary and select secondary endpoints. The primary endpoint of cCR12 is defined by the proportion of patients who maintain their clinical complete response for 12 months after 6 months of dostarlimab. This is is assessed at the 18th-month time point of the study. Secondary endpoints include event-free survival at 3 years and also cCR36, which is assessed at the 42nd-month time point in the study. Additionally, we will assess overall survival and assess specific

survival at 5 years.

To conclude, the GSK study is designed to evaluate a curative potential of dostarlimab monotherapy for this disease. If the MSK results are confirmed, this therapy could change the treatment paradigm with an approach that would both improve cure rate and avoid the debilitating morbidities of the current standard of care.

Because of this ambitious effort, we have designed our phase 2 study with rigor supported by data and with thorough planning and preparation. We solicited and integrated feedback from global experts and collaborated with academic institutions like MSK, as well as with patient advocacy groups and regulators. We look forward to generating additional data in this larger patient population to establish the efficacy, safety, and tolerability of dostarlimab as neoadjuvant treatment for patients with this rare form of rectal cancer.

Now, Dr. Abdullah will discuss our commitment to accelerated approval in this indication.

Applicant Presentation - Hesham Abdullah

DR. ABDULLAH: Thank you, Dr. Diaz-Padilla.

I'll begin by emphasizing our team's strong interest in collaborating with all stakeholders as we seek to potentially change the treatment paradigm in this indication. The GSK phase 2 study, together with the results from the Memorial Sloan Kettering trial, are designed to support accelerated approval for patients with locally advanced dMMR/MSI-high rectal cancer. This is based on the primary endpoints of a sustained clinical complete response, cCR12, which is reasonably likely to predict for a survival benefit.

At the time of our submission, we will have data from our GSK sponsored study, plus longer-term outcomes from the Memorial Sloan Kettering trial, giving us information on the benefit-risk in at least 130 patients. The goal is to provide a potentially curative therapy and survivorship that spares patients the devastating long-term effects of surgery, chemotherapy, and radiation. The plan

is to follow an accelerated approval with a complete data conversion package that includes a supportive phase 3 trial in another stage II and III dMMR/MSI-high population. The submission would also include longer follow-up from both the MSK study and GSK's pivotal trial, including available survival data. We are in discussions with FDA now regarding the separate, large, randomized trial in patients with dMMR/MSI-high perioperative colon cancer.

Let me speak for a moment about the role of the study in supporting our phase 2 rectal cancer trial. First, rectal and colon cancer are highly similar diseases in terms of their symptoms and biology. Second, both studies will only enroll a biomarker-selected population of patients whose tumors are dMMR/MSI-high. Third, tumor tissue from both colon and rectal cancer that are dMMR/MSI-high are known to be highly responsive to anti-PD-1 therapies, with durable responses observed across multiple tumors.

Lastly, since a randomized study is not

possible in the rectal setting, undertaking one in locally advanced dMMR/MSI-high colon cancer is the closest setting where the benefit of dostarlimab in dMMR rectal cancer can be assessed in a controlled trial.

Here's a preliminary schematic for the proposed phase 3 colon cancer study. This randomized, open-label trial will investigate whether perioperative use of dostarlimab could replace standard-of-care adjuvant therapy. Importantly, the epidemiology of colon cancer, with a higher incidence than rectal cancer, supports the randomized design. That also enables a formal comparison of dostarlimab monotherapy against standard of care in a dMMR patient population, with appropriate primary and secondary endpoints assessed.

To conclude, our phase 2 study is designed with an objective evidence-based approach to appropriately evaluate the benefit-risk of dostarlimab for patients with locally advanced dMMR/MSI-high rectal cancer. The study population

has been selected based on the known high sensitivity of early-stage rectal cancers to immunotherapy. The preliminary evidence from the MSK study supports this. The study design provides non-operative management for patients who achieve a clinical complete response. As Dr. Smith reviewed, this can be safely undertaken when combined with close monitoring, and the GSK study does this for 5 years.

We've established cCR12 as the primary endpoint, and initial assessment of a clinical complete response itself is predictive of favorable long-term outcome. The additional requirement of remaining in cCR 12 consecutive months surely meets the threshold of being reasonably likely to predict clinical benefit. Finally, longer term outcomes from the phase 2 trials and our proposed phase 3 study in colon cancer will support these results.

Thank you. Let me now ask Dr. Vlahovic to conclude our presentation.

Applicant Presentation - Gordana Vlahovic

DR. VLAHOVIC: Thank you.

I am Gordana Vlahovic, and I am the dostarlimab development lead for GSK. The FDA has posed several discussion topics. We have worked to address each in our presentation, and I have summarized them here.

Importantly, Study 219369, together with MSK study, will allow us to adequately assess the benefit-risk of dostarlimab in at least 130 patients. Our application will include long-term safety, response, and survival data based on several clinical endpoints, including cCR12, cCR36, EFS 3, and overall survival.

Thank you. I can take questions now or later.

DR. GARCIA: Thank you.

If there are no further presentations from GlaxoSmithKline, we're going to move forward and proceed with our guest speaker presentation with Dr. Kimmie Ng.

Dr. Ng?

Guest Speaker Presentation - Kimmie Ng

DR. NG: Hi, everyone. Thank you so much to

the FDA for inviting me to give an objective overview of the published literature in regards to the strengths and limitations about the current management of stage II to III rectal cancer. This is the outline of my talk. Because not everybody in the room is a GI oncologist, I will give some basic background on rectal cancer, review the data underlying current treatment paradigms, and then talk about some of the existing data supporting a non-operative management approach, and then end with future research directions.

Colorectal cancer is a huge problem in the United States, as well as globally. Currently, it is the third leading cause of cancer in both men and women, and approximately 30 percent of colorectal cancers are rectal cancer, for a total of about 46,000 new cases anticipated to occur in 2023. Of this population, MSI high accounts for a very small proportion of all of these rectal cancers.

According to the available literature, approximately 2 to 3 percent of all rectal cancers

are MSI high, and it is thought that almost all are due to Lynch syndrome. I want to point out that young onset rectal cancer has been increasing across the last few decades, and MSI high does seem to be enriched in these young patients. Colon rectal cancer is also a leading cause of cancer-related deaths in the United States, and if you combine both men and women together, it is actually the second leading cause of cancer-related deaths, trailing only lung cancer.

Currently, the staging and workup of colorectal cancer is according to the AJCC TNM stage classification, where different from other tumors, the key stage of the primary tumor is determined not by tumor size, but rather by depth of invasion through the wall of the colon or rectum. The N status is determined by the number of regional lymph nodes involved, and M status by the presence or absence of distant metastases.

Because of the complicated staging of rectal cancer, an MRI of the pelvis is critical for accurately staging patients to determine treatment

options. An MRI is the best modality to determine both the T and N stage, as well as assess the circumferential resection margin status, which is a predictor of local recurrence. Endorectal ultrasound can also be done if an MRI is contraindicated. CT scans of the chest and abdomen are required to determine the M stage. A CEA tumor marker level from the blood is also required for prognostication, and every patient diagnosed with colorectal cancer should undergo mismatch repair testing in order to determine the appropriate treatment option.

Very critically, especially for stage II to III rectal cancer, a multidisciplinary team evaluation is absolutely important given the complexity of the different treatment paradigms in this disease. Key members of the team include medical oncology; radiation oncology; colorectal surgery; radiology; and many others that I do not have room to list here. This talk will focus, again, on the management of stage II and III rectal cancer, which is defined by a T stage of T3 or 4 or

by node-positive status.

In terms of the current treatment paradigms, this is the latest NCCN guidelines for the treatment of stage II and III rectal cancer. You can see that two different treatment approaches are endorsed, with the preferred strategy being a total neoadjuvant therapy or TNT approach, where all treatments, including chemotherapy and radiation, are given up front prior to surgery, and two different sequencing algorithms are recommended here. The historical standard of care for many years has previously been long-course chemoradiation or short-course radiation, followed by surgery, followed by post-operative adjuvant chemotherapy.

I'll now briefly go into some of the data supporting these approaches, starting with the historical standard of care, which was established by the German Rectal Cancer Study Group trial published in the New England Journal of Medicine back in 2004. This study compared a preoperative chemoradiotherapy approach to the previous standard

of a post-operative chemoradiotherapy approach. In terms of the primary endpoint of 5-year overall survival, you can see there was no significant difference in the two treatment approaches, with a 5-year OS of 76 percent.

Disease-free survival at 5 years was also not different, at about 68 percent, but interestingly, 5-year local recurrence was significantly lower with the preoperative chemoradiotherapy approach compared to post-op chemoradiation, and this led to this paradigm being adopted as the standard of care. Five-year distant recurrence rates were not different between the two groups either at 36 percent.

Ten-year follow-up of this trial was published in the JCO in 2012, and again, in terms of the endpoint of overall survival, no significant difference between the two treatment arms was seen, nor in disease-free survival. Ten-year distant recurrence rates estimated were at 30 percent, and it is notable that 8 percent of these distant recurrences did occur after 5 years. In terms of

local recurrence, the benefit in favor of a preoperative chemoradiotherapy approach was maintained after longer follow-up with significantly lower rates at about 7 percent in favor of the preoperative approach. Also of note here, 12 percent of local recurrences did occur late after 5 years, so this is a disease that is characterized by not infrequent occurrences of late relapse.

The interest in total neoadjuvant therapy emerged for several potential advantages, including improved tolerance and completion of the prescribed chemotherapy when given up front prior to surgery. TNT does result in higher rates of down staging, which may facilitate R0 resections, and there does seem to be higher rates of pathologic complete response with the TNT approach, which enables the potential for non-operative management. Patients treated with TNT have lesser time with a diverting ileostomy, which is quite significant for these patients, and theoretically, earlier administration of systemic chemotherapy may better address

micrometastases and improve outcomes.

For this reason, several randomized-controlled trials, phase 2 and 3, have been conducted comparing a TNT approach to the historical standard of care. I've selected some of the larger ones here with the Spanish study being the only phase 2 study, and the rest being phase 3. You can see that the sample sizes are different across the different trials. The eligibility is also different across the different studies, with RAPIDO and the POLISH study having high-risk populations.

The TNT approach being investigated was also quite variable among the different studies, with variations in the type of chemotherapy administered, with an intense regimen of FOLFIRONOX tested in the PRODIGE trial, and then long-course chemoradiation versus short-course chemoradiation and different sequences of therapy. The administration of adjuvant chemotherapy was also either mandated or not mandated, and administration of this was variable across the studies as well.

This heterogeneity may have led to the conflicting data on some of the oncologic outcomes.

In terms of 3-year disease-free survival, you can see that the majority of studies did not show a significant difference in favor of TNT in regards to 3-year disease-free survival. The RAPIDO study and the PRODIGE study did show significantly better disease-free survival in favor of TNT, however, most studies did not show corresponding benefit in 3-year overall survival. The POLISH study, which had a benefit initially at 3 years, did not have a benefit after 8 years of follow-up.

What does seem to be consistent is that pathologic complete response rates are higher with the TNT approach compared to standard of care. There does not seem to be any significant difference in 3-year local regional relapse or 3-year distant metastasis in most of the studies, although the RAPIDO trial just seemed to show a benefit of lesser distant metastases with that regimen, though this was a higher risk patient

population in that study.

So what can we conclude from all of these heterogeneous studies? The benefits of TNT do seem to be higher pathologic complete response rates, better compliance with the prescribed chemotherapy, and improve disease-free survival seen in some studies. There are some disadvantages, though, including that earlier stage patients may be overtreated with the TNT approach, where some of them may not actually need chemotherapy. There does not seem to be a difference in sphincter-sparing sparing surgery rates or ileostomy rates, and there is no overall survival benefit.

Therefore, there is insufficient data to conclude that a TNT approach is superior to standard of care, and this is consistent with the NCCN guidelines that continue to recommend both algorithms. Again, there's no significant difference in locoregional failure and inconclusive data on 3-year disease-free survival; we don't yet have long-term outcomes in regards to DFS or

overall survival; and the trials are quite heterogeneous as discussed, making it difficult to make definitive conclusions. Importantly, there are no known biomarkers to date to better select who would benefit most from a TNT approach.

So despite the fairly good outcomes for patients with multimodality therapy, unfortunately treatments for rectal cancer, according to these paradigms, is extremely toxic, and this has been reviewed already. The several components of the treatment algorithm result in significant rates of bowel dysfunction, urinary dysfunction, sexual dysfunction, infertility from pelvic radiation, and permanent ostomies, which then can result in body image issues and depression; and these can all negatively impact quality of life.

Consequently, there is interest in de-escalating therapy while trying to maintain efficacy for patients with stage II and III rectal cancer. One option is to try to eliminate radiation from the treatment algorithm. The FOWARC trial, published in JCO in 2019, compared the

standard historical approach of long-course chemoradiation, followed by surgery with adjuvant chemotherapy with two different types of chemotherapy regimens, and compared that to a chemotherapy-only approach, where radiation could be administered, but at the discretion of the treating investigator. In regards to the primary endpoint of 3-year disease-free survival, there was no significant difference between 3 arms, nor in the 3-year locoregional relapse rate, or overall survival, which is certainly intriguing in terms of whether or not radiation can be eliminated for selected patients.

More data to inform this very important question will hopefully be forthcoming in the PROSPECT trial for which we hope to have data later this year. This is a completed phase 2/3 trial of selective preoperative radiation for upper rectal tumors that are not T4 or N2. These patients were randomized to the historical standard of care compared to a chemotherapy-only approach, followed by selective radiation for those who have

suboptimal response. All patients then go to surgery, and post-operative treatment is at the discretion of the treating investigator.

Then finally, another approach to de-escalation is to try to remove surgery from the treatment algorithm, and interest in this came from initial retrospective studies from Dr. Habr-Gama and resulted in this publication of long-term outcomes from the large international multicenter observational registry study called the International Watch and Wait Database. Of note, this was a heterogeneous study population due to being a registry study, where there were many earlier stage patients included in this study.

There was non-uniform staging and response assessment methods, and variable treatment strategies were utilized, including sometimes only with radiation alone and oftentimes not with both radiation and chemotherapy. However, the results are shown here and do seem promising for a non-operative management approach. 880 patients who were able to avoid TME and had a complete

clinical response were included in the trial, and after a median follow-up time of about 3 years, the 2-year tumor regrowth rate was 25 percent. Five-year disease-free survival, distant metastasis rate, and overall survival all seemed very favorable in patients managed with the watch-and-wait approach.

To characterize further the time course of the tumor regrowth, 64 percent were diagnosed within the first year, with the vast majority occurring by 2 years after completion of treatment; 18 percent of the people who also had tumor regrowth had distant metastases as well. The vast majority were able to receive TME, as well as some receiving local excision, and most of these tumor regrowths were able to be successfully salvaged. In terms of distant metastases, only 11 percent occurred within the first year and only half within the first 2 years. Three-quarters were diagnosed by 3 years after completion of treatment.

Because of this initial promising data, multiple randomized trials are now going on,

testing non-operative management compared to standard of care, and these trials are selected once here for stage II or III rectal cancer. You can see that, again, the treatment schedules being tested are all quite variable, with variations in whether it's long-course chemoradiation or short-course radiation being tested, as well as the sequencing of the various therapies. The response assessment time point is also variable, ranging from 12 weeks after treatment start, up to 38 weeks after treatment start, and the primary endpoints upon which these trials were designed were also different across the studies.

This is a graphical representation of the variability in the endpoints and the time of response assessment. You can see the different treatment regimens being tested in these trials, the variability not only from time of treatment start to response assessment but also from completion of radiation to response assessment, which we think may potentially impact outcomes as well; and the primary endpoints were also different

as well as when they are being assessed.

Of these trials, only the OPRA trial has been completed and published, and I will spend a little bit of time describing this important study. This was a phase 2 randomized, multicenter trial that tested two different TNT approaches: induction chemotherapy, followed by long-course chemoradiation, and a non-operative management approach for those who achieved complete clinical response, versus a consolidation chemotherapy approach, thus started with long-course chemoradiation, then chemotherapy, and then, again, non-operative management if a complete clinical response was achieved.

The primary endpoint was 3-year disease-free survival compared to a historical control from the TNT studies just reviewed of 75 percent. These are the data out of 324 patients. The median follow-up time was 3 years, and 3-year disease-free survival was 76 percent. Although this is technically a negative study because it wasn't superior to the historical control, it is reassuring that a

non-operative management approach can result in similar disease-free survival to some of the prior TNT studies that included surgery.

Local recurrence-free survival and distant metastasis-free survival were also quite favorable and, again, pretty consistent with prior TNT studies. The time point of response assessment, as mentioned, was 34 to 38 weeks after treatment start, and clinical complete response rates were also high at about 75 percent. Tumor regrowth happened significantly more in the induction chemotherapy arm compared to the consolidation chemotherapy arm, but half the patients were able to achieve 3-year organ preservation in the consolidation chemotherapy arm.

This trial is important because it does provide the first benchmark data from a prospective randomized study on clinical complete response rates and organ preservation rates with a TNT approach. The other strength of the study is that it is the first to mandate uniform assessment of response at a specific time point and according to

specific criteria for definition of a complete clinical response. This is outlined here, and follows the MSK regression schema used in other studies.

The surveillance of patients undergoing non-operative management was also very rigorous and uniform across patients and involves frequent surveillance, especially within the first initial years after completing treatment. This is important due to the time course of tumor regrowth and recurrence rates seen in these patients, managed by watch-and-wait approach.

The majority of tumor regrowth and local recurrences do occur within the first 2 to 3 years of completing TNT, as you can see from these curves. Local recurrence-free survival does seem to plateau out, again, at about the 2-to-3-year mark. Distant metastases-free survival seems to take a little bit longer to plateau out, at about the 3-or-4-year mark.

Another important question is, what happens to patients who are managed for a complete clinical

response by watch and wait, who then have a tumor regrowth compared to those who undergo immediate surgery after restaging with an incomplete clinical response? You can see here from these curves that there is no statistically significant difference in disease-free survival between these two populations; numerically, though, the disease-free survival does seem to be a little bit lower as time goes on for the watch-and-wait patients.

In terms of the types of recurrences that happen after TME for immediate restaging, or TME after a period of clinical complete response followed by regrowth, there again is no statistically significant difference in the types of recurrences seen in these two patient. Populations. Sample sizes are small, though; and if you note the numbers here, they do seem to be numerically higher for local and distant recurrences among patients treated with a watch-and-wait approach but, again, sample sizes are extremely small.

In terms of the type of surgery received in

these two populations, slightly more patients who were treated with the watch-and-wait approach and then had tumor regrowth underwent APR with permanent colostomy compared to those who underwent surgery immediately after restaging.

The important questions of whether outcomes of watch and wait are equal to patients who do undergo immediate surgery with pathologic complete response unfortunately have very little data to provide any answers, but from this meta-analysis of predominantly retrospective studies, it does seem encouraging that those managed with the watch-and-wait approach do not seem to have significant differences in non-regrowth recurrence rates or cancer-specific mortality.

There did seem to be in this study improved disease-free survival for those undergoing surgery as opposed to managed with the watch-and-wait approach, though; but overall survival was not significantly different between these two populations. Ideally, what we would like to see with long-term data are patients with a sustained

clinical complete response having equivalent overall survival to those who undergo surgery with a pathologic complete response.

The other relevant question is what happens to patients who do have clinical complete response but who undergo surgery anyway versus are managed by a non-operative management approach? And again, from this meta-analysis of mainly retrospective studies, there does not seem to be any significant differences in outcomes between these two patient populations, but certainly prospective, more rigorous data are needed to more definitively answer this question.

So that brings us to the dostarlimab trial for which you have already heard a lot about. The primary endpoint for this study is MSI-high stage II to III rectal cancer patients, with overall response rate of 6 months per the MSK regression criteria, or a past-year or clinical complete response at 12 months.

In the initial set of patients, there was a really promising 100 percent clinical complete

response rate with median follow-up of 6.8 months. As mentioned already, though, there are some limitations to this very promising data, including currently still a small sample size and short-term follow-up. This is a single institution study with extensive expertise in non-operative management, and there is no data on other clinically relevant endpoints or long-term data, which GSK is planning to address with their package.

The importance of the endpoints cannot be overstated, and an international consensus group was convened to try to standardize these endpoints and the definition of these endpoints across trials that are testing non-operative management. They recommend that for phase 1 and 2 trials of treatment intensification that clinical complete response be used as the primary endpoint. For phase 2 and 3 trials, 3-year organ preservation rate was recommended as the preferred endpoint, and they note that, critically, secondary outcomes such as anal/rectal function, toxicity, and quality of life absolutely need to be assessed in these

trials.

They also have some recommendations on the optimal response assessment time point because, again, that could influence complete response rates as well as ultimate outcomes; also, a strict schedule of surveillance for patients undergoing non-operative management approach is also provided in these consensus recommendations as well.

To summarize the data on non-operative management, I quoted this footnote that is now included in the NCCN guidelines for rectal cancer because I think it does give a fair summary of where we are to date with the existing data. The NCCN now recommends that for patients who do achieve a complete clinical response with no evidence of residual disease, as determined by digital rectal exam, MRI, and endoscopic evaluation, that a watch-and-wait approach can be considered in centers with multidisciplinary teams, but we do not yet know what the risk of local and distant failure may be, relative to those patients undergoing standard treatment algorithms.

Surveillance needs to be rigorous and frequent, and include digital rectal exam, protoscopy, and then imaging as well, especially in the initial first few years.

So where do we go from here? The upcoming JANUS phase 2 rectal cancer study in the U.S., led by Dr. Joshua Smith, just recently activated and will provide further important data on clinical complete response, as well as a non-operative management approach with TNT treatment. This trial will test long-course chemoradiation first, followed by two different chemotherapy regimens, to see if an intensified chemotherapy of FOLFIRONOX will improve response rates and lead to more non-operative management. The primary endpoint of this trial is complete clinical response.

The other important data that we'll be able to get from the JANUS study is data on whether or not this approach can be replicated across various cancer care settings. This is run through the intergroup and cooperative groups of the NCI, where a vast majority of the enrollment centers are in

the community setting. So again, the feasibility of this approach will hopefully be able to be provided to us from this study.

Other remaining questions include what are the long-term disease-free and overall survival outcomes? Does non-operative management actually result in improved functional outcomes and quality of life, given that radiation is still included in these TNT approaches? Are there biomarkers, importantly, such as circulating tumor DNA or radiomics that can better predict who would benefit from a non-operative management approach, and what is the optimal surrogate endpoint for these trials? As alluded to already, can this approach the replicated and feasible in a community setting?

We do know from European data that centralized multidisciplinary care and centers of excellence are associated with improved outcomes in patients with rectal cancer. Those who are treated by a colorectal trained, high volume surgeon do better with decreased perioperative morbidity, decreased stoma rates, and improved disease-free

and overall survival. Back in 2011, a consortium called OSTRiCh was convened to quantify the quality and uniformity of rectal cancer care in the U.S. at the time, and very concerningly, they saw significant variation in the use of neoadjuvant treatment, and noted that a vast majority of patients were not being treated in high volume centers.

So there is now a national accreditation program for rectal cancer to hopefully try and more uniformly provide quality care to all patients with rectal cancer. In this one study that evaluated over a thousand hospitals to see their readiness for meeting these national accreditation standards, which are quite rigorous, unfortunately, only about 3 percent of these hospitals actually met these thresholds for five of the selected criteria. They also very concerningly noted disparities in the types of centers that were ready for accreditation, being enriched in academic centers, high volume centers, as well as those that serve mainly highly resourced, high socioeconomic status populations.

There are no outcome data yet, but hopefully that will be forthcoming soon, and currently only 75 programs are accredited. But there is significant concern about making sure that this accreditation program does not widen disparities in access to care and that all patients with rectal cancer have equal access to high-quality care. Thank you very much for your time.

DR. GARCIA: Thank you, Dr. Ng.

We will now proceed with the FDA presentation from Dr. Sandra Casak.

Dr. Casak?

FDA Presentation - Sandra Casak

DR. CASAK: My name is Sandra Casak. I'm a pediatric oncologist and the acting team leader for the gastrointestinal malignancies team in the Division of Oncology 3. These are the FDA staff involved in the preparation for this meeting.

During my presentation, I will discuss the following: background on locally advanced rectal cancer and treatment options; dostarlimab's development in patients with dMMR/MSI-high locally

advanced rectal cancer; and today's topics for discussion. I will now summarize some epidemiological facts about rectal cancer and discuss the current treatment options for locally advanced rectal cancer.

Approximately 46,000 new cases of rectal cancer are expected to be diagnosed in 2023 in the U.S. Overall, up to 20 percent of patients with colorectal cancer have dMMR/MSI-high tumors, but these tend to be more frequent in early stages and in right-sided tumors. There are conflicting data on the incidence of dMMR/MSI-high rectal cancers, and in the literature for rectal cancers, the reported incidence of dMMR/MSI-high ranges from 2.7 to 21 percent.

The standard of care for treating locally advanced rectal cancer, irrespective of dMMR/MSI-high studies, consist of multimodality therapy that includes fluoropyrimidine-based chemotherapy, radiation, and surgery. The intent of treatment is curative. As you heard in Dr. Ng's presentation, there are several treatment

strategies with different sequencing of each component of therapy, differences in length of treatment, intensity of chemotherapy, and radiotherapy, et cetera.

Overall, local recurrence rates range from 5 to 20 percent, and between 15 and 30 percent of patients develop distant metastases. The disease-free survival at 3 years in modern trials using TNT ranges from 56 to 76 percent depending on population studied and clinical strategies employed, with survival at 3 years at approximately 90 percent.

The prognostic and predictive role of dMMR/MSI-high in rectal cancer is not well characterized. The slide shows a retrospective analysis of patients with deficient and proficient mismatch repair rectal cancer treated at Memorial Sloan Kettering who were matched based on baseline tumor and demographic characteristics.

Patients were treated with neoadjuvant FOLFOX or fluoropyrimidine-based chemoradiation. As shown on the figure on the left, a higher rate

of progression was observed in patients with deficient mismatch repair versus the mismatch repair proficient counterparts receiving initial treatment with FOLFOX. As shown on the right, no patient experienced disease progression before surgery, while or after undergoing chemoradiotherapy. The pathologic complete response for patients with deficient mismatch repair or their proficient controls were similar; however, as noted, this is a small retrospective study, and results should be interpreted with caution.

In another retrospective analysis of patients treated at MD Anderson Cancer Center, patients with dMMR/MSI-high stage II-III rectal cancer were treated with fluoropyrimidine-based neoadjuvant chemotherapy and radiation therapy. Of the 29 patients who underwent surgery, 28 percent had a pathological complete response. One patient had a clinical complete response and declined surgery. The authors concluded that fluoropyrimidine as a radiosensitizing agent for

dMMR/MSI-high rectal cancer seems to be associated with favorable pathologic response.

Treatment with chemotherapy, radiotherapy, and surgery can adversely impact the quality of patients survivorship. The rates for long-term treated-related complications are difficult to estimate due to differences across studies on patient populations and treatments used. Following radiotherapy and surgery, bowel dysfunction is common in up to 52 percent of patients having reported to experience low anterior resection syndrome characterized by fecal and flatus incontinence, urgency, and frequency. In addition, up to 79 percent of patients have urinary and sexual dysfunction, and for primary treatment of the tumor, or as a consequence of the complication, some patients require permanent ostomies. Infertility has also been reported as a treatment sequelae.

At some institutions, a non-operative approach may be offered to some patients following completion of neoadjuvant chemotherapy and

radiation therapy if a complete, or sometimes near complete, clinical response is observed. Patient selection for a non-operative approach is not standardized, and different tumor characteristics have been used to determine eligibility for this approach, including tumor size, presence and absence of lymph nodes, relationship with other anatomic structures, et cetera.

There is also marked heterogeneity across studies not only due to differences in study populations, but differences in outcomes studies; the chemoradiation and chemotherapy regimens used; schedules of assessments; imaging protocols; follow-up protocols; et cetera, which limit interpretation of data from these trials.

The evidence supporting the non-operative management derives mostly from non-randomized retrospective studies. As such, there is limited evidence from randomized-controlled studies that characterizes the relationship between clinical complete response and long-term outcomes. Available data from small series using variable

chemotherapy and radiotherapy regimens demonstrated clinical complete response rates ranging from 10 to 78 percent. Of note, in studies exploring non-operative management, patients received local therapy with radiation.

The observational registry study of the International Watch and Wait Database included 880 patients with locally advanced rectal cancer who underwent non-operative management after an observed clinical complete response. The incidence of local regrowth was 25 percent with 88 percent of local relapses occurring by year 2 following initiation of non-operative management. In this retrospective series, the five-year-old survival rate was 85 percent.

In another retrospective series of 113 patients treated at Memorial Sloan Kettering with clinical complete response following chemoradiation and chemotherapy, and who were managed following non-operative management approach, the local relapse rate was 19.5 percent; 81 percent were able to forego the resection of the

rectum and 18 percent required total mesorectal excision, or TME, for management of relapse. The 5-year overall survival in this cohort was 73 percent.

As mentioned before, data from the non-operative management studies are difficult to interpret because among other factors, there is heterogeneity in patient population included in studies and heterogeneity in results based on treatment strategy. The randomized OPRA study is an example.

The figure on this slide shows the study design, which compared two different sequencing of treatment strategies, induction chemotherapy followed by chemoradiotherapy versus consolidation chemotherapy after chemoradiotherapy. After restaging, patients that had a clinical complete response, or near complete response, were offered non-operative management.

As you can see on the table, of the 225 patients in both arms who went into non-operative management, 40 percent in the

induction group and 27 in the consolidation group developed tumor regrowth during follow-up compared with 6 percent of patients who underwent surgery after chemo and radiotherapy.

Please note the population for which non-operative management was offered those patients with clinical complete response and patients with near complete response, which highlights some of the heterogeneity described before. Also, as Dr. Ng showed, disease-free survival at 3 years was 76 percent in both arms, but there is a difference between the rate of local regrowth observed in each treatment strategy, favoring early use of chemoradiation. This highlights the differences in outcomes related to treatment modalities described before.

Data for outcomes in patients with dMMR/MSI-high locally advanced rectal cancer who were managed with no local therapy is mostly limited to the Memorial Sloan Kettering study 19-288, which has been previously presented today. As presented at ASCO, 14 of the 18 patients

involved were evaluable for disease response after completion of dostarlimab treatment. All have clinical complete response; all patients, the response was ongoing. Fourteen of these patients had a sustained response for 12 months or more, and as reported at the ASCO GI Symposium last month, more than 30 patients have already been involved.

To summarize, standard of care for locally advanced rectal cancer combines chemotherapy, radiation, and surgery with curative intent. Outcomes are viable, depending on the study population, treatment strategy used, and endpoint definition. As the precise estimates are not available, treatment for locally advanced rectal cancer with standard of care is associated with significant morbidity. Data evaluating the dMMR subset are limited and suggests similar responses to patients with proficient mismatch repair when exposed to radiotherapy.

Based on mostly retrospective data, non-operative management of patients with locally advanced rectal cancer with a clinical complete

response after neoadjuvant therapy is available in selected patients and institutions; however, there are no standard criteria to identify appropriate candidates for a non-operative management treatment strategy, definition of clinical complete response, outcomes, frequency of monitoring, et cetera.

The major risks of a non-operative strategy are the potential risks for tumor distant spread among patients with an apparent complete or near complete response who are initially observed and the risk of excess rates of tumor regrowth that would require more aggressive surgery or that cannot be resected. In addition, there is lack of information on long-term outcomes from randomized trials.

I will now summarize the proposed dostarlimab clinical development in patients with dMMR/MSI-high locally advanced rectal cancer. GSK plans to develop dostarlimab as a single agent for the treatment of patients with locally advanced, treatment-naïve, mismatch repair deficient or microsatellite instability-high rectal cancer.

This slide summarizes the proposed clinical development program to support a future supplemental BLA for this indication. The package intended for accelerated approval will include data from the upper and middle rows of the table. These are single-arm studies evaluating dostarlimab as a single agent in a combined 130 patients with dMMR/MSI-high stage II-III rectal cancer, with clinical complete response at month 12 or cCR12 as a primary endpoint.

Following an accelerated approval, GSK plans to submit the results of analysis of clinical complete response at month 36, or cCR36, and event-free survival at 3 years as secondary endpoints to verify clinical benefits, along with other secondary endpoints, including total mesorectal excision-free survival, disease-specific survival, and overall survival. In addition, shown in the bottom row of the table, data from a randomized-controlled trial in locally advanced dMMR/MSI-high colon cancer patients may be submitted as supportive evidence.

As presented by GSK, Study 219369, or Study 2, is intended for registration of dostarlimab for the proposed indication. This is a global, multicenter, single-arm study that will involve approximately 100 patients with previously untreated disease.

This study has been previously described by GSK, so I will briefly go over it, but wanted to show that for patients who do not achieve a clinical complete response rate at the time of the first assessment, those patients with near complete response or incomplete response, if the patient and the investigator agree to delay in implementing standard-of-care treatment, a second assessment, including rectal MRI endoscopy and CT scan, will be performed at least 4 weeks and no longer than 8 weeks after the prior assessment.

If a clinical response is achieved then, the patients may proceed to non-operative management instead of standard of care. If the patient has any response less than a clinical complete response, or if they do not undergo the second

assessment 4 to 8 weeks after the end of dostarlimab treatment, they will proceed to standard-of-care therapy.

Non-operative management will consist of watchful waiting with regular assessment for recurrent disease as follows. In years 1 and 2, patients will be assessed with endoscopy rectal MRI and CT every 4 months. In years 3 to 5, this assessment will be conducted every 6 months. If at any time a patient develops evidence of recurrent disease during the non-operative management period, they will be evaluated for salvage therapy by the local care team and will transition to standard of care.

The primary endpoint is clinical complete response at 12 months. cCR12 is defined as no evidence of residual disease by endoscopy, rectal-specific MRI, and no evidence of metastatic disease 12 months after the first post-treatment clinical complete response assessment by Independent Central Review. Key secondary endpoints are cCR36 as assessed by Independent

Central Review, defined as maintenance of clinical complete -- [inaudible - audio gap].

I will start over with the definition of cCR36. cCR36 is defined as maintenance of clinical complete response for 36 months and event-free survival at 3 years by investigator assessment, defined as remaining alive and free of disease progression precluding surgery, local recurrence, and distant recurrence. Overall survival at 5 years will also be assessed.

I will now introduce the topics for discussion. As you heard from Dr. Fashoyin-Aje's introductory remarks, there are several aspects of the dostarlimab program in rectal cancer that require further consideration and centered on: the adequacy of the proposed single-arm trial to evaluate the efficacy and safety of dostarlimab, including the long-term benefits and risks of treatment; the proposed clinical endpoints, clinical complete response rates, and event-free survival to characterize and verify the benefits of dostarlimab, including the proposed timing of

analysis; the study population with dMMR/MSI-high stage II-III locally advanced rectal cancer for a non-operative management approach; and the potential impact of the variability in care and expertise across multidisciplinary staff and across study sites on study conduct, and eventually on outcomes.

The first topic of discussion is the adequacy of the proposed single-arm trials to evaluate the efficacy and safety of dostarlimab, including the long-term benefits and risks of treatment. Approximately one-third of new cancer indications have been approved based on single-arm trials evaluating response rate; however, FDA has generally required randomized-controlled trials to support approvals in the curative setting where a comparative assessment to standard of care can be performed and endpoints of clinical benefits such as survival can be evaluated. Analysis of survival outcomes are uninterpretable in single-arm trials. Additionally, single-arm trials generally do not reliably characterize drug effects on symptoms or

function.

The available data that describes outcomes following non-operative management are derived mostly from retrospective series from highly specialized centers. These series evaluate different outcomes in heterogeneous populations who received various treatments and often challenges. As such, there are currently no benchmarks in patients with locally advanced rectal cancer for whom some type of local treatment with earlier therapy has been omitted or deferred.

GSK states that conduct of a randomized trial in patients with dMMR/MSI-high locally advanced rectal cancer is infeasible, citing the rarity of the disease and the high rate of clinical complete response observed in the available preliminary data from the Memorial Sloan Kettering trial, which may be leading to lack of interest in a trial comparing dostarlimab with standard-of-care treatment. It is not clear that dMMR/MSI-high locally advanced rectal cancer is so rare as to preclude the conduct of a randomized study.

Diseases with lower incidence have been successfully studied in the randomized setting.

Although preliminary clinical data in 18 patients are promising, cautious consideration of whether this data may preclude the conduct of a randomized study is warranted. Given these limitations, we would like the committee to discuss the use of single-arm trials in the curative-intent setting, as a comparative assessment to standard of care cannot be performed, and evaluation of time-to-event endpoints and other important information about outcomes to characterize clinical benefit may not be interpretable without a comparator arm.

The second topic for discussion is the adequacy of the proposed clinical endpoints, clinical complete response rates, and event-free survival to characterize and verify the benefits of dostarlimab, including the proposed timing of analysis. GSK proposes clinical complete response at 12 months as assessed by Independent Central Review as the primary endpoint for the proposed

single-arm trials intended to support a future marketing application for accelerated approval.

In oncology, the efficacy endpoint most frequently used for accelerated approval in solid tumor malignancies is a durable response rate. The response rate is a reliable marker of drug activity since malignant tumors generally do not shrink without therapeutic intervention. However, the overall response rate, there's an uncertain relationship to improvement in overall survival in diverse cancer types.

GSK proposes to use clinical complete response and event-free survival at 36 months to verify the clinical benefit of dostarlimab if accelerated approval is granted. As previously discussed, analysis of long-term survival outcomes such as event-free survival and overall survival is uninterpretable in the absence of concurrent control. Additionally, evidence supporting the non-operative approach is derived mostly from non-randomized, retrospective studies.

As you heard today, there is marked

heterogeneity across studies, which limit the interpretation of data from these trials. We would like the committee to discuss the limitations of historical data on clinical complete response rate as endpoint for locally advanced rectal cancer therapy; the magnitude and durability of clinical complete response reasonably likely to predict clinical benefits; and the interpretability of event-free survival as an endpoint of clinical benefit in a single-arm trial.

The third topic of discussion is related to the study population with locally advanced rectal cancer for a non-operative approach. Patients with Stage II-III locally advanced rectal cancer are typically treated with standard-of-care sequencing chemotherapy, radiation, and surgery; however, the presence of lymph nodes and/or large tumors may signal a higher risk of recurrence. Additionally, it isn't clear to what degree patients with clinical disease features that may confer higher surgical risk or higher risk of recurrence -- for example, stage presence of Lynch syndrome -- have

been included in or excluded from studies evaluating the non-operative management.

The criteria to select patients for non-operative management have not been established. As such, discuss whether a prespecified number of patients at higher risk of recurrence -- for example, those with clinical T4 or node-positive disease -- should be studied in the proposed trials to permit a benefit-risk assessment in the heterogenous, locally advanced rectal cancer population.

The fourth topic for discussion is related to the potential impact of the variability in care and expertise across multidisciplinary study staff and across study sites on study conduct, and ultimately on outcomes. Irrespective of the treatment strategy used, studies have shown that patients treated at high volume centers with surgical expertise and specialization in the treatment of locally advanced rectal cancer have better outcomes such as higher rates of sphincter preservation, decreased rates of post-operative

morbidity and mortality, lower rates of local recurrence, and improved survival compared to those treated at lower volume centers.

Non-operative management requires intensive follow-up to facilitate early recognition of local or systemic recurrences and to increase the chances of a successful salvage treatment. It is recommended that a multidisciplinary team be involved in the care of patients with locally advanced rectal cancer, particularly when implementing the non-operative management strategy, as patients with locally advanced rectal cancer represent a heterogeneous group with respect to risk of recurrence.

In Study 2, and if approved in the real world, patients will be followed across centers with variable experience with a non-operative management approach. The results of the preliminary evaluation of dostarlimab in dMMR/MSI-high locally advanced rectal cancer indicate high clinical complete response rates. These results are based on a single institution

trial conducted in a high volume center with the expertise to provide non-operative management as a treatment option to patients.

Study 2 is a global, multicenter study that will involve 100 patients, 30 of whom will be enrolled in the U.S., including at Memorial Sloan Kettering. It isn't clear the extent to which data will be generalizable to a broader population treated in centers with variable expertise in managing locally advanced rectal cancer using a non-operative management approach. Discuss any specific recommendations for site selections to characterize the benefits and risks of treatment with dostarlimab for this indication across diverse clinical centers.

To conclude, GSK is developing dostarlimab as a single agent for the treatment of patients with locally advanced, treatment-naïve, mismatch repair deficient or microsatellite instability-high rectal cancer. However, there is uncertainty regarding the efficacy of non-operative management in locally advanced rectal cancer given the

heterogeneity of data supporting this approach, the paucity of data for patients with dMMR/MSI-high locally advanced rectal cancer, and patients who have not received prior therapy.

In addition, there are also uncertainties on the adequacy of the proposed data package to permit a benefit-risk assessment for the proposed indication. We seek to gain the committee's input on the proposed data package for a future dostarlimab application to support accelerated approval for this indication and to subsequently confirm clinical benefit. Considering these issues, FDA asks the committee to vote on the following.

Will the data from the proposed single-arm trials, enrolling a total of 130 patients, be sufficient to characterize the benefits and risks of dostarlimab in the curative-intent setting for patients with dMMR/MSI-high locally advanced rectal cancer? Thank you for your attention.

Clarifying Questions to Presenters

DR. GARCIA: Thank you, Dr. Casak.

We will now take clarifying questions for the presenters, GlaxoSmithKline, LLC; guest speaker; and FDA. Please use the raise-hand icon to indicate that you have a question and remember to clear the icon after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

So maybe I'll start with a comment, then a question, before the group and the committee start asking or commenting on presentations that we just heard.

So it is clear to me that I recognize how unlikely it would be for patients with

MMR-deficient and MSI-high locally advanced rectal cancer to be randomized, their willingness to be randomized to a surgical arm if such a trial existed. I also recognize that although JANUS is a well-designed, well-thought-out trial, it does exclude patients with this biology, if you will, with MMR and MSI-high disease. So I'm not sure that JANUS will be applicable for the patients in question today.

A question for Dr. Ng and Dr. Smith from the surgical perspective and also from the medical oncology perspective, as both of you are experts in this field, I recognize -- and GSK has expressed in their presentation -- that there is an international consensus panel that has been reluctant to do or move forward with a randomized study designed precisely because of the potential for low accrual.

But if the question for me is surgery and the ability, we're asked, to lead to a durable complete response, quote/unquote, "cure," that may delay or avoid perhaps the morbidity and potential

detriment in quality of life with a surgical approach such as the TME and/or LAR, why would not -- and again, I'm not a GI medical oncologist, but from the drug development perspective, why not do a randomized trial where we look at the I-O approach with dostarlimab against a chemo RT approach with an endpoint of complete clinical response, and only then decide who are the patients who actually may not be or may be ideal candidates for non-operative management?

Dr. Ng and Dr. Smith, if you can comment on that or perhaps answer that question.

DR. NG: Sure. This is Kimmie Ng. I can start. I do agree that a randomized clinical trial is not likely to be feasible in this population for many of the reasons that have already been presented. There is just such limited data on how these MSI-high rectal cancer patients do with standard of care, although much of the data suggests they don't respond very well to chemotherapy but may still respond quite well to chemoradiation.

The problem is the toxicity of radiation, and I think with increasingly large numbers of young patients being diagnosed with locally advanced rectal cancer, many of whom do want to preserve their fertility, for example, it will be very hard, in my opinion, to randomize to a chemoradiation arm.

DR. GARCIA: Thank you, Dr. Ng.

Dr. Smith?

DR. SMITH: I'm here, yes. I'll just speak to your comment about the inability to randomize patients to a watch-and-wait arm. We know from the design of the JANUS trial, in addition to the design for the OPRA trial, speaking of patients, in addition to our own experience off protocol, patients will not be randomized at the clinical achievement of clinical complete response; they would not be willing to be randomized to watch and wait at that time.

So I think it's a very important point that you bring up, and I completely agree with what Dr. Ng just stated. I think she's right on point

there, and I agree with what she said.

DR. GARCIA: Thank you.

We have some questions from our committee members. We'll start with Dr. Ciombor.

DR. CIOMBOR: Thank you. Yes, I have a couple of clarifying questions for GSK about the 219369 study design, specifically, a couple of detailed questions.

Will you require central confirmation of MSI-high status or deficient mismatch repair, and what do you anticipate in terms of the global reach of this study? You mentioned that there would be more than 45 sites. How do you anticipate that being distributed across the world?

DR. VLAHOVIC: This is Gordana Vlahovic. I'm the dostarlimab development lead here, and I do have Dr. Alvarez, a pathologist, to answer your first question.

DR. ALVAREZ: Hi. My name is JD Alvarez. I am the head of precision medicine at GSK, and I am trained as a medical pathologist. In this trial, we are allowing local testing for enrollment, but

we are centrally confirming using an FDA-approved companion diagnostic, the VENTANA MMR IHC.

DR. VLAHOVIC: This is Gordana Vlahovic. If I can answer your second question, can you please repeat? Were you asking about global representation or sites for states or out?

DR. CIOMBOR: My question was how do you anticipate the distribution of sites, either selected or participating, in terms of -- obviously, you're hoping to have global representation, which is wonderful, but any ideas of how many sites will be opened in various regions of the world for this study?

DR. VLAHOVIC: Yes, we do. For now, feasibility is still ongoing, so we are still looking into some countries, additional countries and sites, but for now we have 10 countries and 43 sites that we have identified already.

DR. CIOMBOR: And what's the --

DR. VLAHOVIC: I'm sorry. Global means the United States, we are going to Europe, and we are going to Asia as well.

DR. CIOMBOR: Do you anticipate that most of this will be ex-U.S. or --

DR. VLAHOVIC: It is a small study, and we are aiming at adequate representation in the totality of the number for U.S.

DR. CIOMBOR: Thank you. That answers my questions.

DR. GARCIA: Thank you.

We'll move forward with our next ODAC member, Dr. Madan?

(No response.)

DR. GARCIA: Dr. Madan, maybe you're in mute.

(No response.)

DR. GARCIA: Alright. In the interest of time, we'll move on then.

Dr. Nieva?

DR. NIEVA: Thank you. Jorge Nieva, USC. I have two questions. The first is for Dr. Cercek, and the second is for the GSK team.

For Dr. Cercek, how many people enrolled in the MSK study failed to complete 6 months of

therapy? What was the screen failure rate and what was the dropout rate? And maybe we'll stop there, and then I'll ask the GSK team question.

DR. CERCEK: Thank you. To date, all patients have completed all 6 months of therapy. We have not had to stop therapy early. The screen failure rate was 3 patients total out of the 30. As you could probably imagine initially -- and the drop rate, rather. Initially, the patients were unsure, so some patients proceeded with standard of care; however now we are enrolling all patients that present because of their willingness and interest in enrolling.

We have had 3 fails. Two were IHC positive, and then on repeat were actually not mismatch repair deficient, and then one patient was mismatch repair deficient -- rather, was mismatch repair proficient, but rather than MSI, so this patient should have been enrolled, and then was not, and was treated with standard of care off study.

DR. NIEVA: Then for the MSK team, I was wondering what the proposed failure looks like in

the 219369 study. We have from OPRA 2 a 75 percent cCR rate, cCR12 rate. Would you propose non-inferiority in the design to 75 percent? What in a single-arm study looks like failure? Why don't we start there?

DR. VLAHOVIC: I'm going to invite Dr. Chen, who is our statistician, to address your question?

DR. CHEN: Thank you. Tai Chen, GSK statistics. The study was designed to assume a cCR12 rate with a certain precision. Currently, we have 130 patients, and with 130 patients, the maximum width of the confidence interval would be approximately 20 percent. So let's put this in perspective. If we have a cCR rate of 85 percent, the lower bound of the confidence interval will be approximately 75 percent. Thank you.

DR. NIEVA: Thank you. We heard from Dr. Cercek the challenges with interpretation of the biomarker. What are going to be the standards for biomarker interpretation for both eligibility, as well as for being evaluable for the primary endpoint?

DR. VLAHOVIC: We will enroll based on the local testing when available, and if not available, we're going to use a central testing, and central testing also will be provided, but at the end of the study, as a part of the bridging study as a confirmatory study. So we will enroll patients based on the local or central testing, and we will also analyze the patients with all of them enrolled as eligible for a study within our denominator.

DR. NIEVA: And will that central review be something that is done by an outside vendor where GSK is blinded to that determination or is GSK going to be informed of that determination when deciding on eligibility?

DR. VLAHOVIC: If local testing is not available, the central testing will have to be provided for eligibility. So yes, that information will be provided. After the study is done and completed, that particular information of the rest of the patients tested with local testing and having confirmatory central testing will be provided only after the study's done.

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

DR. GARCIA: Thank you.

We'll move forward with Dr. Kunz.

DR. KUNZ: Great. Thank you. This is Pam Kunz. I have a question for Dr. Ng, and it's specifically on slide 31 regarding the consensus guidelines.

I have a question about the recommended endpoint, and wondered if you could just review it. It looks like from the slide that the phase 1/2 trials has a cCR as the recommended primary endpoint to enable evaluation of non-operative management, and then phase 2/3 have organ preservation. And I'm just wondering if you could comment how this relates to the proposed trial. Thank you.

DR. NG: Yes. Thank you for your question. I do think it's something that probably does need to be taken into consideration as you consider what the ideal endpoint is for a trial that's being proposed. It does seem to be a phase 2 trial. It

isn't intensifying therapy, though, in order to enable non-operative management; but again, it's a different biology that's being studied here and a different type of therapy that is being studied.

I think the consensus group did recommend that for larger phase 2/3 trials, where standard of care is being changed, that 3-year organ preservation rate is the endpoint that is recommended.

DR. KUNZ: Okay. Thank you.

DR. GARCIA: Thank you.

We'll move to Dr. Conaway.

DR. CONAWAY: Yes. Mark Conaway. Yes. I had a couple of questions. One question is about the feasibility of the randomized trial. The colorectal trial does have a randomization, both arms having surgery, though one is delayed.

Can you expand a bit on why randomization is feasible in that population and not in the rectal cancer population?

DR. VLAHOVIC: Sure. We do not actually re-randomize in colon cancer, as we believe that

the surgery, which is part of both arms, experimental and control, is something that we still were not ready to avoid in that population. And the reasons why are because non-operative management has been long studied in the rectal cancer patients; as the surgery, though, is significantly more complex and associated with significant comorbidities, which on the other hand, colon cancer has a surgery that is less complex and certainly is associated with less comorbidities.

But just to come back to what's really important here and why did we choose the colon cancer as the confirmatory study is we are talking about -- [audio feedback]. Okay. I am so sorry. I heard an echo, and I thought you asked me to stop.

We are actually selecting very homogeneous populations because both colon and rectal are dMMR/MSI-high selected phases 2 and 3. They are very similar when it comes to their biology. They have a historically already metastatic setting established, very good responses, and sustained

responses to immunotherapy, and both dMMR/MSI-high in colon and rectal have data supportive, not suboptimal, and less susceptibility to chemotherapy. Furthermore, rectal is more rare. There is a high incidence of colon cancer, therefore randomization itself seems more plausible. Thank you.

DR. CONAWAY: Thank you.

My next question for anyone on the GSK team, I heard the word "representative sample" for the future 100-participant trial. How will you know or how will you design the trial to ensure that happens?

DR. VLAHOVIC: Are you applying to diversity of the population? Can you please clarify the question for me?

DR. CONAWAY: I would just clarify the question. Is there enough known about the population of dMMR/MSI-high locally advanced rectal cancer patients to even know if this is a representative sample, and to know if the information you're getting out of that study is

somehow representative of a larger population?

DR. VLAHOVIC: To begin with, the dMMR/MSI-high population is rather small. If you look at the numbers, databases, even the numbers, the database we've used or FDA used, when it comes to the prevalence of dMMR/MSI-high is it is a lower percentage. So therefore, we are talking in the U.S. between 2[000] and 4,000 at the best case.

What's really important to mention is there is data out there in the metastatic setting, in the dMMR/MSI-high population, that is strongly supportive of usage of immunotherapy in that population, where the responses were shown to be significantly better than what we see with standard of care, and very importantly, those responses are sustainable responses.

DR. CONAWAY: Okay. Thank you. That answers my questions.

DR. GARCIA: Thank you.

Dr. Vasan, do you have a question?

DR. VASAN: Hi. I had a question for Dr. Ng, and this is about slide 26 in your slide

deck. I'm just still trying to make sense of using cCR as an endpoint and the role in locally advanced rectal cancer; I guess just two questions.

The first is this says that patients that sustain cCR should have an equivalent overall survival. We've seen this in the slide above, and I recognize that these are small numbers. We have a DFS; the DFS is favoring surgery, and I think in a lot of the other retrospective or single-arm historical studies, it seems that the cCR rates are still associated with reasonably high DFS rates.

Do we have any evidence, just overall, that cCR really correlates with improved DFS in this disease? Then the second question was, in the IWWD cohort, were their patients in that cohort who had Lynch syndrome or MSI-high rectal cancer, and if we have any of those subset analyses?

DR. NG: Hi. Thank you for your question. To address your first question, do we have enough data that cCR actually does correlate with increased survival, long-term survival, we don't have robust prospective data. The data that has

been cited largely stem from single institution retrospective studies such as from Brazil, including some patients in the international watch-and-wait database that, in general, had fairly favorable staging to begin.

The patients in that study also had variable staging methods. Many were not staged with MRI, for example. The treatments were highly variable. Some only received radiation and not what we would consider the modern standard of care. But in those studies, it did show that those who did have cCR seemed to have better outcomes. But again, these are not data from prospective studies.

In regards to your second question about how many patients in the international watch-and-wait database did have Lynch syndrome, I don't think that data is available, at least not in my recollection of reading those papers.

DR. VASAN: Thank you.

DR. VLAHOVIC: Gordana Vlahovic here from GSK. Please, would you allow me to invite Dr. Smith? He would like to add to that answer as

well.

DR. GARCIA: Sure.

DR. VLAHOVIC: Thank you.

DR. GARCIA: Dr. Smith, you can move on.

DR. SMITH: There are actually data from prospective trials. The German trial has long-term data suggesting and showing fairly definitively that there are path CR data demonstrating and supporting the data that I showed in my presentation. In association with clinical complete response, I showed the high rates of disease-free survival, and in the German trial where patients all went through surgery and then had pathologic complete response, meaning no tumor in the resected specimen, high rates of disease-free survival.

So it's a correlation there, but I think there are data to support that when you have a complete response, there's a strong association with disease-free survival.

DR. VASAN: Well, I agree with pathologic complete response. I think the data suggest that

that is true, But my question is really about the clinical complete response, which is really the endpoint in question here.

DR. SMITH: Right, and the data that I showed, just to come back to the prospective data from OPRA, and then of course the retrospective data that I also showed, in OPRA, the strongest prospective data is showing clinical complete response and a strong correlation with disease-free survival, shown here with clinical complete responders having 84 percent at 3-year disease-free survival compared to the incomplete responders.

DR. VASAN: Thank you.

DR. GARCIA: Thank you.

Dr. Madan, are you back? You can ask your question.

DR. MADAN: Yes. I'm sorry for the technical issues. I have a question for Dr. Ng first, and then the sponsor.

For Dr. Ng, I think you said this -- and I just want to clarify I understood this. But it seemed like the best data to evaluate the CR and

its potential impact was at 2 to 3 years. Am I correct in interpreting your presentation? Or you can correct me if I'm not. Thank you.

DR. NG: Thank you. In terms of the best time point to evaluate clinical complete response, I showed some data that suggests that tumor local regrowth can still occur at a significant rate up to 2 years after completion of TNT, and rectal cancer does tend to be a cancer that does have later recurrences, so I do think longer term follow-up is important. That being said, there are also data about durability of response for MSI-high tumors that has been shown in metastatic disease, so MSI-high patients may be a different population.

DR. MADAN: Okay. Thank you for clarifying it.

Then for the sponsor, forgive me if you mentioned this, but what is the timeline you think it would take to accrue to this trial, as you planned it so far? Thank you.

DR. VLAHOVIC: I'm sorry, Dr. Garcia, or Dr. Madan. Would you please repeat the question?

DR. MADAN: Yes. What is the timeline to completing accrual to the trial you've proposed, in your second trial?

DR. VLAHOVIC: Right. Accrual time for our 100-patient proposed study is about 14 months; so 14 months, and we are planning to obviously do the follow-up as proposed, as you've seen in our study design. Just as a reminder, cCR12 happens, or assessment is at 18 months from the beginning of the study.

We will also continue with data collection and follow-up on those patients, and we will have data from cCR. We will have at 36 months, at 42 months, and the 5-year at 60 months. We will continue with following patients and collecting all the data points. Thank you.

DR. MADAN: Thanks.

Then one question I guess for the sponsor or the experts; what do we know about heterogeneity of the disease at this early stage in patients who may have MSI-high but also foci that are not MSI-high, and then therefore may not respond to this therapy?

Kind of a general question for the sponsor and the experts. Thank you.

DR. VLAHOVIC: Thank you, and I will invite Dr. Cercek to address this question.

DR. CERCEK: I think heterogeneity has certainly been described. It's incredibly rare. We have not seen it to date in our patient population, but I think that will be an important thing to keep in mind going forward. However, just generalizing MSI patients in general, immunotherapy is extremely effective. What we've seen so far in the neoadjuvant studies -- not just in the rectal study that we presented today, but in colon cancer as well -- as we mentioned, the responses, pathologic complete responses to immunotherapy, are really very significant. Thank you.

I don't know if there was a second part to your question.

DR. GARCIA: Dr. Madan, is your question answered?

DR. MADAN: Yes. That answers my question.

DR. GARCIA: Thank you, Dr. Cercek. Thank

you, Dr. Madan.

Maybe we'll go to the FDA review division.

Do you guys have a question or comment?

DR. FASHOYIN-AJE: Yes. Good morning. This is Dr. Fashoyin-Aje. We want to have a couple of our staff here provide some additional comments to some of the questions that have been posed. As a start, I think it's really important that we make sure that we all have a clear baseline in describing or characterizing the available data that would inform an assessment of the correlation between clinical complete response rate and long-term endpoints. I think, as you heard from all of the presentations today, there's really a scarcity of data, and the data that is available is quite heterogeneous.

So I think it's important that, really, this discussion be informed by, really, a clear understanding and collective agreement of actually what the data represent. So I will first start by turning it over to some of our statistical colleagues to comment on some of the responses with

respect to clinical complete response rate and relationship to long-term outcomes.

DR. MISHRA-KALYANI: Hi. This is Pallavi Mishra-Kalyani from FDA statistics. There was some discussion regarding the data available to characterize the association of complete response rate, or clinical complete response rate, and DFS or other long-term endpoints. So far, I think we just want to be very clear that the data that has been shown and the associations that have been found are from retrospective studies and mostly responder analyses, which are very hard to trust with regards to demonstrating anything other than potential correlation.

We do need more data preferably from randomized studies, and certainly multiple studies would be very helpful in a meta-analysis to really identify whether or not there's true association between these endpoints or if what we're seeing is just the improved outcomes due to gradients of response.

So as Dr. Fashoyin-Aje has just mentioned,

there is very little data available, and from our perspective, as regulators and as statisticians, there's certainly not sufficient information available to demonstrate or consider an association at this time between these endpoints.

DR. FASHOYIN-AJE: Thank you, Dr. Kalyani. I will now turn it over to Dr. Steven Lemery.

DR. LEMERY: Hi. Thanks for acknowledging me. This is Steven Lemery, DO3. I just wanted to make two points. One regarding testing was brought up earlier, and we do feel that that's a very important point to bring up.

The Sloan Kettering experience, my understanding, patients undergo testing with the MSK impact panel, which assesses patients for mutations in the dMMR proteins, as well as microsatellite instability and tumor mutation burden. So I think you're pretty certain that those patients who are treated in the trial have dMMR or microsatellite instability.

I think there may be a concern for patients who may get tested in local settings. If there's a

false positive in this case, it's going to be bad because the patients are going to be delaying definitive therapy that they would otherwise be receiving with chemoradiation. So testing, we do find to be an important aspect of the care of these patients and a necessary component to ensure that these patients have accurate tests for this disease, so the committee members may want to talk about that.

The other issue that was asked to the company was about the representativeness of the patient population. I think there are multiple layers to that, and we want the patients to be representative as far as the racial and ethnic profile of patients in the U.S. But beyond that, we want the patients to be representative of the patients with the stages of tumors whom may benefit or not from from receiving a treatment, especially in rectal cancer.

Patients with a T4 lesion may be very different in this setting than a patient with T3. It is good to know, regarding nodal disease, that

most of the patients from the Sloan Kettering study had node-positive disease, so that gives you one level of comfort, but it would be helpful to know the number of patients who had N2 and 3 disease, which may be much higher risk compared to patients who had N1 disease.

I think it will be important, especially if the company is seeking a broader stage II/stage III indication, to make sure there is a sufficient number of patients with high-risk disease, especially patients with T4, or N2, or N3 lesions, to make sure that the risk-benefit profile is going to be effective in those groups of patients.

DR. GARCIA: Thank you.

For the FDA, do you have any additional comments?

DR. FASHOYIN-AJE: Thank you for now.

DR. GARCIA: Thank you.

Okay. Let's go back to our committee members.

Dr. Chang, do you have a question, please?

DR. CHANG: Great. Thanks so much. This is

George Chang. My question is directed at probably Dr. Cercek, Dr. Smith, and I guess the GSK investigator team.

One of the critical components of a study like this, and has been well described as the primary endpoint, when done well, has a very strong correlation with a pathologic clinical complete response as well. The question has to do with what will be the plan for confirmation of the assessment of clinical complete response at each of the sites.

You are currently planning, on average, approximately 2 patients per site, so are there site qualifiers? Is there central review? What other confirmatory process will there be so that you can assure what is assessed locally as a clinical complete response indeed is, or that further treatment may be necessary? Thank you.

DR. VLAHOVIC: I'm going to start answering this question from GSK. I'm going to invite later Dr. Smith and Dr. Cercek if they want to add anything else, but I would like to introduce Dr. O'Donnell, who is the medical director on our

study, and he will provide you with those details.

DR. O'DONNELL: Hello, everyone. My name is Dr. Sean O'Donnell. I'm a senior medical director here at GSK. To address your question about how we plan to standardize the assessment of cCR throughout the study, we plan to approach this from a number of angles. First and foremost, the primary endpoint of the study, cCR12, will be evaluated by Independent Central Review. We intend to centrally review both endoscopies with full video recordings of the entire endoscopy and a central review of MRIS. We also intend to use the MSK regression criteria, which has been successfully used in the prospective OPRA trial and has been published and used in the community now for close to 10 years.

We intend to train our sites in how best to interpret the assessments. We plan to provide trainings using experts from Memorial Sloan Kettering, both to our central reviewers, as well as to providers in the community, both endoscopists and MRI radiologists, I should say. I'll also

highlight that in terms of our long-term endpoints, the cCR36 endpoint will also be centrally reviewed, so we'll provide central confirmation there.

So in total, we have carefully thought about the ways in which our endpoint can be standardized and used across our global population, and we think that that will provide the robustness and certainty that FDA is seeking.

DR. GARCIA: This is Dr. Garcia. Just a question on your statement as to training sites. Could you explain how do you plan to train for endoscopic assessment? Are you talking about that the MSK group will be leading that effort? Are you planning to have GI people, colorectal people, going to sites in the community to actually train standard GI or surgical people to actually do the scopes? Is that the extent of the training?

DR. O'DONNELL: So the performance of the endoscopy itself is a standardized flexible sigmoidoscopy. The training will be more toward interpretation of the finding, so we will be providing webinars and sessions to educate the

proceduralists who will be performing these endoscopies on what types of features they should be looking for to identify a clinical complete response.

We also hope to leverage a large database of existing data that Dr. Smith has put together to help train providers in the OPRA and JANUS trials to provide additional information to the sites, and we are looking into the feasibility of even in-person opportunities to get them in front of our experts to allow for question and answer.

DR. GARCIA: Thank you.

Any additional comment?

DR. CHANG: May I ask a follow-up question?

Thanks very much. That's very helpful information. I guess the one missing component is the digital rectal exam. How do you plan to standardize and document that?

DR. GARCIA: Would you mind just to state your name for the record so we know who is asking the question?

DR. CHANG: I apologize. This is George

Chang, again, with a follow-up to my earlier question. Thank you.

DR. GARCIA: Thank you, Dr. Chang.

DR. O'DONNELL: Hi. This is Dr. O'Donnell again. Obviously, we can't centrally confirm physical exam findings, but we do plan to gather that data within our database and will use it as part of a sensitivity analysis for our primary endpoint.

DR. CHANG: Thank you --

(Crosstalk.)

DR. GARCIA: Dr. Chang, are you done with your questions?

DR. CHANG: Yes. Thank you. That completes my questions.

DR. GARCIA: Thank you.

We will go next to Dr. Park.

DR. PARK: Hello. This is John Park. I had a question also for the sponsor on the cCR 12-month endpoint. I do share some of the concerns that have already been brought up, but even if it was shown to be a good endpoint, I'm wondering if you

can comment on that we're comparing known treatments that can cure, chemoradiation, with a new single-agent modality that we're not sure can cure. How do you bridge that uncertainty with this endpoint?

DR. VLAHOVIC: Very importantly, I think here, to set the stage, we understand who is really our population, target population. Our target population are dMMR/MSI-high patients who are known to be exceptionally susceptible, regardless even of stage, to immunotherapy. So here we have data not just coming from Sloan Kettering; data that patients with rectal cancer have on monotherapy, exceptional, 100 percent cCR, consecutive cCR. We also have data that is growing and being shared publicly, as recent as ESMO, in early-stage colon cancer, where I-O alone has achieved significant, or 95 percent, responses with actually 67 percent complete pathological response.

So in the setting here where we are talking about different populations, where we know historically that chemotherapy might not be the

most optimal therapy and where we believe that other standard-of-care therapy provides the benefit but also are associated with significant comorbidities, we believe that moving forward with dostarlimab, with our PD-1 inhibitor that has shown cCR thus far, we believe that this is the way to identify or to follow to further prove that those patients could indeed benefit from long-term outcomes and replace standard of care.

I would like to invite Dr. Cercek here, as well, just to reflect and share some of her observations.

DR. CERCEK: I'd like to just add that both in the MSK study, as well as in the proposed GSK study, the endpoint is cCR12; however, patients are not withheld standard of care if they need it. So if a patient does not achieve a clinical complete response after 6 months of dostarlimab, they can undergo standard-of-care chemoradiation and/or surgery as needed. Likewise, they're followed very closely once they achieve a cCR to reach that cCR12 and beyond. So if the tumor regrows, they can

undergo standard of care. Thank you.

DR. PARK: One more related question. Dr. Abdullah did touch on the phase 3 colon cancer trial. I guess there seems to be a little asymmetry because the colon cancer trial has surgery there, which we know can help cure the cancer. This kind of relates to another question. Why not do dostarlimab only for that trial, slide 44, if there's confidence in the rectal cancer setting? Can you comment on that asymmetry?

DR. VLAHOVIC: I think we did address that, at least partially, in the prior answer, but this particular study does have a surgery in both the experimental and control arm. And surgery here, it is something that is being less studied, and surgery by itself is significantly less complex even though it's curative intent and has less comorbidity. We did consult with global experts, and the recommendation to us, or feedback to us, was for this particular population, where non-operative management was not studied and we don't have data versus rectal cancer where we do,

to reserve the surgery as part of the experimental arm.

Now what really is important here in this study, and the information and knowledge that we are going to gain, is the neoadjuvant part of dostarlimab, where we are going to be getting information on the pathological response; and at the end of the day, we compare and we use information, and what we're going to use on this study to reference the rectal cancer is the EFS.

So the magnitude of the benefit of dostarlimab that we will capture from this study would be, in our belief, a good reference that could help actually reassure that benefit we are observing in rectal cancer is true. Thank you.

DR. PARK: Thank you. No more questions.

DR. GARCIA: Thank you.

We'll move on with Dr. Lieu.

DR. LIEU: Hi. This is Chris Lieu. My question is for the FDA, and just trying to wrap my head around the concept of accelerated approval in a curative disease setting. The reason why I ask

is I'm just trying to figure out where the bar is in terms of what the FDA would like to see.

When we think about accelerated approval, we've seen these approvals in regards to overall response rate, and that's been in the metastatic setting, and obviously the corollary here would be complete clinical response. But I just want to get a sense for what the FDA is looking for in the accelerated approval setting given that this is a curative setting and not the typical metastatic disease setting that we've seen previously.

DR. GARCIA: Does anybody from FDA want to address that question?

DR. PAZDUR: I will. This is Dr. Pazdur. Obviously, it has to be higher. Okay? It doesn't preclude the use of accelerated approval because it's a serious and life-threatening disease, but the uncertainty is far more acceptable when you're dealing with patients in a single-arm trial who have no other therapies available to them. And that's the common scenario that we're using accelerated approval in, is the metastatic disease

setting usually in patients that have gone through the available therapies that are here.

Here again, this is the whole reason why we're bringing this to the committee, is what is this risk that is tolerable here, from a regulatory standpoint and also from a practice standpoint? You are dealing with a curative therapy, so there should be greater scrutiny here, and that's why we're bringing this application or this proposal to this committee.

DR. LIEU: That's very helpful. Thank you. I have no further questions.

DR. GARCIA: Thank you.

Dr. Katsoulakis, do you have a question?

DR. KATSOULAKIS: Hi. Thank you. Yes, I guess a couple of questions and maybe then some comments later. I guess there was the question about also doing -- pick possible patients that [indiscernible] MSI-high based on entire classification, and I guess 3 out of 30 patients is about a 7 percent rate, and I worry about that being emphasized later on.

In addition to that, I guess for the initial presentation from the MSK team -- unless I've misread -- I know this was alluded to previously with an N1 versus N2 or 3 disease and how many lymph nodes are involved. Similarly, with T4 disease, I believe there are only 2 patients enrolled from the initial cohort; however, they were sort of lumped in with the T3s. And the T4s traditionally behave very differently, and that's one of the reasons they invade into other organs. That's why we give radiation and local therapy in order to have significant benefit on these patients.

We also know for tumor size, this is a really large bulk of disease. In the metastatic setting, there isn't as much of a response. And while tumor size has been traditionally used for staging, I do wonder about the actual Ts for these patients that were thought to be large tumors, but I didn't see any specific data on that, if that could also be shown. In addition to the nodal status, I think that would be very useful. That's

my first question.

DR. VLAHOVIC: I'm going to invite Dr. Cercek to respond to this question.

DR. CERCEK: In the initial 18 patients -- and Dr. Ng showed this slide as well -- there were 2 patients that had T4 tumors invasive into adjacent organs, into the vaginal canal, and both responded and had a clinical complete response.

We don't grade in regard to the node status. We've, as a field in general, moved towards node positive, but we did look at that, and about half, if not over half, of the patients had N2 disease. There were large, bulky tumors to a significant extent, and it continues to be what we're seeing.

DR. KATSOULAKIS: But you will be including T4 patients based on 2 patients that had a complete response. I just wanted to clarify.

DR. CERCEK: Yes.

DR. KATSOULAKIS: I just worry about delaying their care as well if we know that chemoradiation as the center [indiscernible]

modality generally responds well for them, for those patients and the ones that may be misclassified. I do have concerns about delaying their care in micrometastatic disease, and what that means to them long term.

My other question I guess was also some of the PANDORA [ph] trials use ctDNA. I just was wondering if you're going to be also using other blood markers in addition to that.

DR. CERCEK: Yes. I can answer that in the MSK studies, we are enrolling T4 patients. The patients are followed very closely on treatment to ensure that we're not missing progression. They have an endoscopic exam at 6 months and then at 3 months -- sorry, rather at 6 weeks and then at 3 months they have a full assessment with an endoscopy/MRI, as well as imaging, CT/PET, to assess for metastatic disease; and then again at 6 months at the completion of therapy, and then every 4 months thereafter in follow-up.

DR. KATSOULAKIS: So PET CT scans will also be incorporated, and not just CT scans.

(Crosstalk.)

DR. CERCEK: Yes.

DR. KATSOULAKIS: And then I just wanted to make sure because oftentimes we pick up micrometastases that CTs do not, so I just wanted to just ask on that as well.

DR. CERCEK: Yes. In the MSK study, we are doing PET CTs. This was a research question initially when the trial was designed, borrowing a bit from the metastatic study because normally in rectal cancer, the assessment is just the CTs, and we're actually finding that the CTs on the MRIs are adequate to assess response in rectal cancer, even in this patient population.

DR. KATSOULAKIS: Then finally, also --

DR. CERCEK: And just to follow up your other question -- I apologize -- the ctDNA, we are collecting ctDNA at all time points that we've been assessing. We have not yet evaluated it, but that will add additional data as to the clearance of ctDNA, and as you said, the potential risk of micrometastatic disease and eradication.

DR. KATSOULAKIS: I think those were the PANDORA trials that used it, I think, for the earlier responders. I think that was a marker that they used, but you can double-check that, but that's what I believe I was reviewing.

Then my last question, I guess, is if this does go through, how will you assess whether this versus other PD inhibitors, like nivolumab or pembro, will have equivalent CR rates? As they're all being studied, will there be equipoise amongst them, or is this one supposed to be the winner? And if it is, how will you compare dostarlimab if this goes through for accelerated approval? Is pembro just as effective or whatnot? Thank you. That ends my questions.

DR. O'DONNELL: Hi. This is Dr. O'Donnell again from GSK. I wanted to take an opportunity to clarify the answers to your questions that you asked as they pertain to our study. We will be performing the same assessment schedule that Dr. Cercek was in terms of close follow-ups. We will also be performing endoscopy at 6 weeks, and

endoscopy, MRI, and CT at 12 weeks, and then again at the end of treatments. We will also be assessing ctDNA at a variety of time points throughout the study to look at response, as well as potentially recurrences later down the road.

In terms of your question about the role of dostarlimab versus other PD-1s, we can only answer the questions that we have in front of us, and we know that the data that we are following up on are with our drug, so that's one that we can develop and speak to. We think that we are optimistic that we will be able to recreate what Dr. Cercek has shown.

DR. KATSOULAKIS: There's a nice editorial by Rene Persaud [ph] that was published recently, just discussing clinical trial design and also reviewing dostarlimab versus other PD-1 inhibitors, and what a clinical trial design would look like. It was very nice.

I also did want to say as a radiation oncologist that radiation has evolved over time, and that the toxicities are much less than they

used to be, and some of the reports are a little outdated using some of the 1970s data, I believe I was reviewing. I just wanted to add that. Thank you.

DR. VLAHOVIC: Thank you.

DR. GARCIA: Thank you.

Dr. Pazdur, I see your hand is up. Do you have a question or a comment?

DR. FASHOYIN-AJE: Actually, it's Dr. Fashoyin-Aje from the FDA. May I ask a question?

DR. GARCIA: Please, go ahead.

DR. FASHOYIN-AJE: So I just wanted to follow up on the issues around training and expertise at the local levels, and I wanted to ask Dr. Cercek, and maybe Dr. Ng, to comment on the imaging protocols and whether or not one can reasonably expect them to be the same in the highly specialized centers versus other centers, and then ask GSK to comment on any training they may be providing to ensure adequate evaluation of the MRI imaging as part of the assessment of the endpoint.

Thank you.

DR. VLAHOVIC: Dr. Ng, do you want to answer first or do you prefer that GSK goes first?

DR. NG: I can answer quickly first.

Being from a large academic medical center, I have limited experience with what the imaging capabilities are of some community centers in other parts of the country and the ability of the radiologists, but I can say that at least with all the community centers affiliated with our institution, they are all adequately trained to be able to do this.

Again, this is where I think the JANUS trial will be really useful because that's conducted through the cooperative group sites, many of which are in the community, and we will be getting valuable information there about the quality of the reads and assessments from that study.

DR. VLAHOVIC: Now to share his perspective on the training, since he has actually done the training of the other investigators on OPRA.

DR. SMITH: This is Dr. Smith. We will use

training similar to what we did for OPRA and what we're doing in JANUS, and I'll echo what Dr. O'Donnell brought up earlier about the central review of both the endoscopy and the MRI, and bringing in experts both with use of online tools and webinars to train the centers, which we found can be very helpful in this regard, and enforce the use of standardized consensus criteria, which is very helpful in determining cCR as we move forward in a prospective trial.

DR. GARCIA: Thank you.

Dr. Kunz, do you have your hand up? Do you have another question?

DR. KUNZ: I do. Thank you. This is Pam Kunz. I have one more question for GSK.

We talked considerably about patient preference in terms of the design and how a randomized design may be impractical due to that. I'm wondering if you could speak to the degree of patient input from patient advocates that you had in the design of the study. Thank you.

DR. VLAHOVIC: We have collected feedback

from multiple experts throughout actually the globe regarding the preferences of the participation in such a study and recommendation to their patients to be enrolled in such a study in randomized fashion versus single arm. It was almost a unanimous response based on the rarity of this disease, all the comorbidities coming from the treatment, and all the data, actually, and after publicly shared, all the responses and awareness of the data. The physicians, or experts, were not necessarily in support of the randomization, and for those reasons, we felt that it's not feasible.

I will also invite our medical director here, who actually did have communication with a lot of those exports, to share his experiences.

DR. O'DONNELL: Hi there. In addition to the external experts from around the world that Dr. Vlahovic mentioned, we also presented this design of the study to GSK's patient-expert council, which is a group that represents patients in the community. I can also ask Dr. Cercek to come and speak regarding the interactions that she

has with patients and the advocacy that her patients have done on behalf of this idea.

DR. CERCEK: Thank you. I can just add to that, that as I described initially, when we opened the study in late 2019-2020, we did have a couple patients that chose to proceed with standard of care. Since the data became publicly available, we have been actively sought out, and I think our accrual attests to that, where we were at 18 in June, and we're now over 30 patients.

So patients are actively seeking us out, are hoping to be mismatch repair deficient when they're diagnosed with rectal cancer, and I think with the knowledge, of course, that they can receive the therapy and potentially not have radiation or surgery. So I believe that, really, a randomized trial would not be feasible.

DR. KUNZ: Okay. That's all.

DR. GARCIA: Thank you.

DR. VLAHOVIC: Thank you.

DR. GARCIA: Dr. Chang, you have your hand raised. Do you have another question?

DR. CHANG: Yes. Thank you. Thanks very much. I just have one more question. One of the real appeals of this approach, of this class of drugs, particularly for this population, is the tremendous demonstrated efficacy and low toxicity in general. This is a question for the GSK team.

Could you speak to dostarlimab and any information you can provide about toxicity data compared to other currently established PD-1 inhibitors? Thank you.

DR. VLAHOVIC: Dostarlimab, overall, the benefit-risk, particularly when it comes to the safety profile, is aligned with all other therapies that are being used and are approved PD-1 or PD-L1 inhibitors. The data that we have is coming from our phase 2 study. We are going to have soon to be shared data from the phase 3 study. But the most frequent, the immune-related AEs, which is about 4 percent, were hypothyroidism, arthralgia, pruritis, and ALT increase, which is very much aligned with what we have seen with other PDXs that are being used for different indications. So

there's really nothing different that can pinpoint or differentiate dostarlimab when it comes to its safety profile from other PDXs being currently approved for different cancer indications.

DR. GARCIA: Dr. Chang, are you satisfied with the answer?

DR. CHANG: Yes. Thanks very much.

DR. GARCIA: Thank you.

Maybe we can move to Dr. Madan.

Dr. Madan, do you have another question?

DR. MADAN: Yes, just a follow-up question for either the experts or the sponsor just so I can have clarity.

I understand the concerns about the randomization of patients and they wouldn't be willing to do it, but can someone let me know if the patients chose not to be randomized to this trial, what would be their standard options outside of the trial? Thank you.

DR. VLAHOVIC: Based on our study design, are you asking what would be the option for the patients that would be enrolled, and then chose to

go standard of care, or what is the standard of care?

DR. MADAN: So my question is, if a patient was provided with the opportunity to do this trial if it was randomized, and one of the concerns that's being raised consistently is that they wouldn't submit to randomization, I'm just trying to understand what would be their path to therapy outside of a trial like this?

DR. O'DONNELL: Hi. This is Dr. O'Donnell again. Patients who opted not to participate in our trial would proceed with conventional standard of care. As was highlighted in our presentations and in a lot of the other talks today, the standard-of-care approach for patients with locally advanced rectal cancers involves some combination of chemotherapy, radiation, and often surgery, so we would expect that patients who didn't participate in our study would proceed with some version of local standard of care, probably chemoradiation, and then potentially surgery.

DR. VLAHOVIC: I would like to invite

Dr. Cercek here just to share her own perspective while this study at MSK was opened, and what patients really were asking regarding all the toxicities, their comorbidities coming from standard of care, quality of life, which were very important in helping them make the decision to actually participate in the study.

DR. CERCEK: The standard-of-care approach for locally advanced rectal cancer is total neoadjuvant therapy with chemotherapy, chemoradiation, and then surgery, and that is what the patients would be offered, and are offered, now off study. And of course, as we've heard, this treatment incurs significant toxicity for the patients, particularly radiation: bowel/bladder dysfunction, infertility, and sexual dysfunction, as well as surgery with very similar toxicities. Chemotherapy as well, although not necessarily as toxic, can result in permanent neuropathy in about 10 percent of our patients, so all three modalities have significant potential toxicity for the patients.

DR. MADAN: Just, I guess, a comment. I think that we're saying that patients wouldn't submit to randomization because they don't want to have surgery, but it sounds like if you were to do a randomized trial, they would either submit to randomization or submit to surgery anyway, unless I'm missing something. And that's the end of my question. Thank you.

DR. O'DONNELL: We would just like to highlight that while randomization to surgery is something that is being resisted throughout the community, we also have noted that resistance to radiation is quite high, and one of the challenges in running a randomized trial in this setting would be the randomization to an arm that would contain radiation and the attendant risks associated with that. So it's not just about randomizing to and away from surgery; it's also randomizing to and away from radiation.

DR. VLAHOVIC: And furthermore -- this is Gordana Vlahovic -- if I may add, the standard of care is combination of chemotherapy, radiation, and

then surgery, if necessary. But just by itself, chemotherapy and radiation was resisted, and radiation because of the significant toxicities that are associated with it and later comorbidities, not to mention secondary malignancies. That is a risk associated with the radiation, but also the fact that we know that the dMMR/MSI-high population is not as susceptible to chemotherapy.

Just for information, for reference, there is a study done by a corporate group in the UK, FOxTROT, that actually demonstrated response to chemotherapy in dMMR/MSI-high colon cancer to be around 7 percent versus, when we looked at MMRP, 22 percent. So in totality, standard of care, as much as it provides success for this early locally advanced rectal cancer, it is also associated with significant comorbidities, and certainly with irreversible change of the lifestyle. Thank you.

DR. GARCIA: Thank you.

Dr. Pazdur?

DR. PAZDUR: First of all, I'd like to

answer Dr. Madan's question. I think many people would use off-label; not that I'm advocating off-label use, but the practical situation would be that many people would consider that, either this drug or another PD-1 drug.

But I wanted to ask some questions of the sponsor. We saw a great deal of variation in how common this disease is, ranging from 3 to 20 percent, which is a huge spread here. What is your current analysis of the landscape here as far as how common this disease is as detected in the primary tumor? Not metastatic disease, primary tumors we're talking about, patients that present with localized disease. How common is this?

Can you give me better numbers than 3 to 20 percent? Because 20 percent could mean that you could do a randomized trial; 3 percent is kind of vague, so to speak, like could it be done? I don't know.

DR. VLAHOVIC: I'm going to invite Dr. Cercek, actually, Dr. Pazdur, if you don't mind, to respond to that question, as she does see

those patients. And she is an expert in the field, so she can provide you with her own perspectives regarding the prevalence, actually, of dMMR/MSI-high in rectal cancer.

DR. CERCEK: Thank you. You're absolutely correct, and I think it's actually probably on the lower end of that spectrum. What we've seen recently in the community, it appears to be about 2.7 percent. Some of those may have also been metastatic, but we believe probably it's on the order of 3 to 5 percent and not some of the higher numbers that were quoted.

DR. PAZDUR: But we really don't know.

DR. CERCEK: We don't know, but we're collecting data as we --

DR. PAZDUR: Okay. So that brings us to how much we know about how this entity behaved clinically. I guess this is a question for GSK.

At the end of the day, I don't know if we're going to be able to do this randomized study in colon cancer, and I'll come back to that point, but others have brought this up. So at the end of the

day, we might be just looking at complete response rate in a single-arm trial, and then having to compare it to an external control.

How much do we know about MSI-high primary rectal cancer and their clinical outcomes treated with conventional, non-operative approaches of radiation therapy and chemotherapy? How many patients do we have here, and what are the clinical outcomes?

DR. VLAHOVIC: I will invite Dr. Cercek to help me to answer this question.

DR. CERCEK: So what we know --

DR. PAZDUR: This is, at the end of the day, something that we might need to really have an understanding of if we're going to be looking at what is the recurrence rate, and what's the clinical outcome of patients treated in this single-arm trial. So what do we compare it to?

DR. CERCEK: Yes. Data are somewhat limited, and they're retrospective. We looked at patients treated with total neoadjuvant therapy, and in our case it was chemotherapy first, followed

by chemoradiation and surgery, and we thought that 29 percent of them -- this was a cohort of 21 patients, but 29 percent of them actually progressed on induction chemotherapy, which was in sharp contrast to the mismatch repair proficient population, where either everyone responded or had stable disease.

In colon cancer, from the FOxTROT study, where patients had resectable colon cancer but they received neoadjuvant chemotherapy, which is our standard 5FU oxaliplatin-based chemotherapy, the response rate in the MSI population, which was about 100 patients, 105 patients, was 7 percent; so really, very poor responses to chemotherapy.

And then again --

(Crosstalk.)

DR. PAZDUR: Okay. So the number of -- yes?

DR. CERCEK: But going back to rectal cancer, we do have data that the patients do respond to chemoradiation, and they can respond, therefore, to a total neoadjuvant package, including chemoradiation.

There was a study from MD Anderson published in 2016, where they looked at 62 patients that received neoadjuvant therapy, and the pathologic complete response rate was 27 percent. So they did respond, but they received radiation. So those are some of the variabilities here in treatment and potential associated --

(Crosstalk.)

DR. PAZDUR: But what were their outcomes after these clinical complete response rates? Did we know that?

DR. CERCEK: We do. The overall survival, I believe, a 5-year survival was close to 90 percent, and there were two other smaller series published each of about 20 patients with mismatched repair deficient cancers, and there was a bit of variability with a DFS of 50 percent, and then an overall survival also in the higher end, I believe 80 or 90 percent; so a small data set, somewhat variable, but --

DR. PAZDUR: So the total end on these data sets are what; the total number of patients we're

basing this?

DR. CERCEK: I would say in rectal totals, about a hundred, maybe a little over a hundred.

DR. PAZDUR: Okay. Okay.

I'd like to go back to GSK about the randomized study that you're suggesting be done. Here again, we've had a lot of discussions about confirmatory trials have to be done in a timely fashion, and one of the reasons that we want trials to be done -- not be done, but to be adequately accruing patients, is can they be done?

Do you actually think that -- I know this has been alluded to by several of the committee members -- there is going to be equipoise here to actively enroll patients? You kind of minimize the aspect of surgery here, and nobody wants a hemicolectomy, and if they could avoid a hemicolectomy, they'll do anything in the world to do that, so to speak. So I'm just wondering, I don't want to agree necessarily to a trial that can't be done.

Do you actually think that over time, if

this drug is approved in rectal cancer, that there will be equipoise; that people will say, "Okay, I'll go on to do surgery," or will they just say, "Okay, I got a CR. I just want to take a wait-and-see approach to this?" What has been your discussion on this? Because I really think people will try to avoid any type of invasive surgery. Obviously, a hemicolectomy, people would want to avoid.

DR. VLAHOVIC: We have considered that. We actually, really, spend a considerate amount of time discussing this particular issue. We have seek-and-receive advice, specifically regarding surgery or no surgery for colon dMMR/MSI-high patients, and interestingly, with all different specialties' feedback and experts in the field. At this point, because of the type of surgery, even though we acknowledge, still, it is a surgery, it would be harder to omit. It is something certainly that we would like to consider to investigate further in a different setting, but for this particular study, the randomization was something

that has been strongly recommended by experts in the field.

Again, we are hoping we rethink and have confidence that we are going to be able to enroll. We are maximizing, actually, the randomization for the experimental arm, and hopefully with that, patients will have a higher chance to receive I-O versus the standard of care, and that's a puzzle.

If I may go back to your first question, I would like to add something else that we are currently doing, and that's something that would probably bring some information regarding the control arm. Right now, we are looking and doing the feasibility of the sites that we have identified where we can actually build an external control arm, particularly in the dMMR/MSI-high stages II and III rectal cancer patients. We have identified 5 sites thus far, and we are planning, when we complete our assessment, to come back to the FDA for further interaction and for your advice.

DR. PAZDUR: But getting back to the

randomized study, obviously this is what your investigators and key opinion leaders tell you now; however, their opinions, as people get more and more experience with treating patients and see that patients are getting complete response, may change, and that's obvious.

DR. VLAHOVIC: Right.

DR. PAZDUR: Wouldn't you agree to that?

DR. VLAHOVIC: Yes, I would. Yes, I would, but --

DR. PAZDUR: And this study may not be able to be done, and I think we just have to be --

DR. VLAHOVIC: Well, but one thing that I would like to say --

(Crosstalk.)

DR. PAZDUR: At this point, we can't. I guess what I'm trying to say is the proof is in the pudding. We'd like to see the accrual on a study like this, and we've made that point very clear that we want confirmatory studies enrolling at the time of an accelerated approval. That we've made multiple times, and it's actually been in recent

legislation.

DR. VLAHOVIC: Dr. Pazdur, if you'll allow me, I would like to invite Dr. Abdullah to actually comment on this question.

DR. GARCIA: Just in the interest of time, perhaps it is acceptable to you, Dr. Pazdur, and to GSK and the applicant, if we can just actually probably just take a break.

DR. PAZDUR: Okay. That would be fine. That's fine.

DR. GARCIA: Thank you.

I think we're going to be able to address and have some clarifying questions after the OPH session, so maybe we can move on so we're not behind.

Well, just simply, we'll now take a 30-minute break. Panel members, please remember that there should be no chatting or discussion of the meeting topic with anyone during the break. We'll resume at -- 30 minutes, that would be around 2:49-2:50; perhaps we can do it so we can get there on time. Thank you.

DR. ABDULLAH: Dr. Garcia?

DR. GARCIA: Yes?

DR. ABDULLAH: If it's ok, it's Dr. Abdullah from GSK. Can I just get 10 seconds only, and then we can go to the break?

DR. GARCIA: I would prefer, if you don't mind, as my prerogative as the chair, just to actually have any other additional comments in the next session, if you don't mind.

DR. ABDULLAH: No problem. No problem.

DR. GARCIA: Thank you. I appreciate it. Thank you all; 2:50 for everybody. Thank you very much.

(Whereupon, at 2:20 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(2:50 p.m.)

Open Public Hearing

DR. GARCIA: We will now begin the open public hearing session.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationships that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment for your travel, lodging, or other expenses in connection with your participation in the meeting.

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

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

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

Will speaker number 1 begin by stating your name and any organization you are representing for

the record?

MS. ROTH: Hi. This is Sascha Roth. I have no financial disclosures. Should I continue?

DR. GARCIA: Please proceed.

MS. ROTH: Alright. My current age is 42. I live in the Washington, DC area, and I now own my family's home furnishing business with my older sister that our parents started in 1991. When I was diagnosed in the fall of 2019, I was originally going to undergo standard-of-care treatment, which was chemotherapy, followed by radiation and surgery and the DC area. I was referred to Dr. Paty, a surgeon at MSK, through a mutual friend who had been treated a year or two prior, and it was serendipitous that this path brought me to MSK.

I quickly learned through genetic testing at Sloan that I had Lynch syndrome, which put me in a situation where standard-care treatment, while being the only option at the time, would not have been a treatment path that would have worked well for me. While sitting in Dr. Paty's office, I was told that standard chemotherapy does not respond

well with Lynch patients, and surgery was not an option based on the location of my tumor, with it resulting in life-altering changes. I was then quickly introduced to Dr. Cercek and her team, and came to find out I was a perfect match for their trial, which was awaiting FDA approval. I put all my faith in Dr. Cercek and her team, and waited a few months until I got the call about 2 months later that the trial had been approved and my treatment could start.

As the way the trial was originally written, I was to undergo 6 months of immunotherapy, followed by radiation paired with a chemo pill, and if needed, surgery would follow. As I started treatment, I was absolutely amazed that immunotherapy did not alter my everyday life. I could go to New York and back and still continue on with my life the way it always was, working out, running a business, and not being compromised by all the toxic effects of standard chemotherapy that I had witnessed other family members experience during their cancer treatment.

Seeing as I worked in DC, I would travel to and from DC to New York every 3 weeks for infusion. At the end of the 6 months of immunotherapy, I made all of my arrangements to move to New York City for the greater part of the summer, while I would undergo chemoradiation.

On the Friday night, before my move to New York City, I got a call from Dr. Cercek that there was no need for me to come. The scans that were done after my final immunotherapy treatment showed absolutely no sign of cancer. I was officially cancer-free, and Dr. Cercek and her team found no need to radiate my body without any sign of cancer. This was not only a relief because I was getting my summer back and I could stay in the comfort of my own home with friends and family close by, but this meant not undergoing radiation and surgery, which would have lifelong effects on my body.

For women that chose not to get an ovarian transposition to move the ovaries out of the radiation field, patients could immediately go into menopause. The ability for women to even carry a

baby after radiation would not be an option through the likely scarring of the uterus. There would also be damage to likely your bladder, sexual function, and the list continues. For me, the greatest gift was being told I was cancer-free, but knowing I would no longer need to radiate my body was a huge relief.

Being as I was the first patient in the trial, nobody knew how this would play out for all the other patients behind me, but each and every patient had complete remission. While I continue to go back to MSK for scans regularly, I feel wonderful. I have no scarring or lifelong issues I need to deal with, but I just have my story to share in hopes that we can gain access for other patients out there just like me. Most stories do not end this way, and I owe measuring [indiscernible] amounts of gratitude to the work of Dr. Cercek and her team.

I want the greatest takeaway from my story to be not only that I was given the gift of this trial, but I was given the gift of achieving

remission without the toxicity of chemo or the scarring effects of radiation and/or surgery. Thank you to everybody for your time, and for giving me the opportunity to share my story. My hope is that we can share many more stories like my own, and people not only in the U.S., but all around the world can celebrate their remission as well. Thank you for your time.

DR. GARCIA: Thank you.

Will speaker number 2 please begin by stating your name and any organization you are representing for the record?

MS. BONITO: This is Kelly Bonito. I have no financial disclosures here from Memorial Sloan Kettering.

I am 31 years old and live in Bradley Beach, New Jersey. My journey with cancer begins with my diagnosis. I was diagnosed with rectal cancer while living in New Jersey, which was soon after moving across country from the west coast and 8 months after having my son. After my diagnosis and doing some research regarding treatment, we

decided that being treated at Memorial Sloan Kettering in Manhattan was my best option. Once at MSK, I was quickly diagnosed with stage III colorectal cancer at 28 years old.

During my first visit with the colorectal surgeon, I was informed that I most likely would never be able to carry another baby because of the damage that would be caused from the radiation. Initially, the traditional FOLFOX treatment was recommended that included chemotherapy, radiation with chemotherapy and surgery. There were three major events with this treatment that would alter my life forever. My uterus would be rendered useless, a colostomy bag, and a significant amount of pain to endure. Thankfully, we had time to work with fertility to harvest my eggs, fertilize, and freeze embryos in hope to expand our family in the future.

My treatment date was looming, and I had appointments with a multitude of doctors at MSK. During one appointment, I was approached by a research nurse with the suggestion of an alternate

treatment plan. They had evaluated my tumor type, and determined that I was a match and candidate for a drug that was in clinical trial. Instead of chemotherapy, radiation, and surgery, I elected to go forward with the alternative option of a clinical trial immunotherapy treatment. The possible side effects were described as far less painful. This sounded a lot better than the traditional treatment, but radiation and surgery were still on the table at that time.

I am patient number 4 in the trial you are speaking about today. After my port surgically was inserted, I started treatment in March. By the second treatment 3 weeks later, I felt 10 times better. The tumor was shrinking, alteration was closing, and my impacted bowels were beginning to clear and re-regulate. By my fourth treatment, I was told that my tumor had reduced by 50 percent, and by my last treatment in August, my tumor had disappeared, and I was declared in remission. Thankfully, I did not have to go through radiation or surgery. It was a true miracle.

I firmly believe and am extremely grateful for the opportunity to receive immunotherapy treatment. This clinical trial and research by the medical community gave me a second chance at life. The immunotherapy provided a medical intervention that did not cause side effects and pain that chemotherapy, radiation, and surgery would have caused in the process.

I'm so happy to report that I'm currently 16 weeks pregnant with a baby girl that is the result of the fertility experts with an embryo transfer. Without this clinical trial treatment, I would have experienced life-altering events that would have not given me the quality of life I now have for myself and my family.

Being diagnosed at 28, making treatment decisions, and having an option has taught me so many life lessons. I know that colorectal cancer is on the rise in young adults, and I hope this clinical trial will be available to many others in the near future. I'm eternally grateful for this life-changing opportunity.

In addition, I appreciate the opportunity to provide my story to you, as I hope it helps you understand why an option like this is important to many other people like me, people who want to live the life they wish to live as a cancer survivor. For my husband and I, that's traveling as much as we can with our family to show our toddler, our new baby, how beautiful Mother Nature is, to teach them about our country and the environment, and about kindness along the way. Thank you all so much for your time.

DR. GARCIA: Thank you.

Will speaker number 3 please begin by stating your name and any organization you are representing for the record?

DR. ZUCKERMAN: Thank you so much. Can you hear me?

DR. GARCIA: Yes, we can.

DR. ZUCKERMAN: Thank you.

I'm Dr. Diana Zuckerman, president of the National Center for Health Research. Our nonprofit research center scrutinizes the safety and

effectiveness of medical products, and we don't accept funding from companies that make those products, so I have no conflicts of interest.

My perspective is based on postdoctoral training in epidemiology and public health; my previous policy positions at congressional committees with oversight over FDA; my previous position at the U.S. Department of Health and Human Services; and as a faculty member and researcher at Harvard and Yale. I'm also a founding board member of the Alliance for a Stronger FDA, which is a nonprofit coalition that urges Congress to provide sufficient appropriations so that FDA can do its very important job.

On a personal note, a close family member recently died of rectal cancer, and I am well aware that this is a terrible disease, and the standard treatment is toxic. A less toxic, equally effective treatment is urgently needed. I find the research promising, but there are too many unanswered questions that two small, single-arm trials can't answer.

Designing a randomized-controlled trial now is our best chance to answer these important questions. These questions will be impossible to answer if the drug is approved for this indication a few years from now, based on the proposed studies, because patients are much less willing to participate in a randomized-controlled trial for a drug approved for the same indication.

I have three points. Number one, the sponsor proposes two open-label single-arm trials. You've heard that it may not be feasible to do a randomized trial. I'm sure it would be difficult, but this specific disease is not so rare that it's impossible. It would be a mistake to give up on a well-designed study without even trying.

There are patients who can only afford good treatment in the context of a clinical trial or who are afraid to deviate from a well-established standard of care when there are no long-term overall survival data for the experimental treatment. The people recruiting patients for the trial would need to clearly explain to patients why

both arms of the randomized trial are good options, a proven treatment versus a promising but unproven treatment. The standard-of-care arm can be smaller than the experimental arm, but the study should be randomized.

Number two. As previous speakers have specified, rectal cancer patients who are treated at the best, high volume medical centers have much better outcomes than other patients. Memorial Sloan Kettering, for example, is not an average cancer center; it's one of the best in the country, and this is another reason why a randomized trial of a representative sample is so important.

My third point. Patients deserve to be able to make treatment decisions based on meaningful clinical outcomes. That's why a solid study design is so important. Overall survival is the key outcome, and quality of life is as well. The new treatment doesn't need to be superior to standard of care, but it does need to be proven to be at least as good.

And beyond the specifics of this FDA

decision, let's think of the big picture. When FDA allows single-arm trials, it sets a dangerous precedent. Future sponsors will try to follow that precedent by also demanding single-arm trials, and FDA will be pressured into making randomized trials optional instead of required. And as we all know, without an appropriate control group, it's not possible to provide the type of evidence that patients and doctors need to make informed decisions. Even relatively small studies with a somewhat smaller randomized-controlled group is better than a single-arm trial. Thank you so much for the opportunity to speak today.

DR. GARCIA: Thank you.

Will speaker number 4 please begin by stating your name and any organization you are representing for the record?

DR. COHEN: Thank you. Good afternoon. My name is Dr. Steven Cohen, and I am a GI medical oncologist at Jefferson Health Abington Hospital and the Sidney Kimmel Cancer Center in Philadelphia. I've been an oncologist for

20 years, and my practice is largely in the community setting and focused on patients with gastrointestinal cancer. I have served as an advisor for GSK in the past, but I am not being compensated for my time today.

As has been eloquently stated, rectal cancer is a major health problem in the United States, and the treatment for locally advanced rectal cancer, which involves the full thickness of the rectum and/or lymph nodes, has historically involved surgery. Over the years, chemotherapy and radiotherapy have been utilized to improve outcomes in addition to surgery; and while potentially curative, as we've heard quite eloquently, the treatments have a large number of acute and chronic side effects, including short-term diarrhea, fatigue, and infection risk, as well as long-term challenges with bowel function, pain, and sexual dysfunction. Thus, the concept of a watch-and-wait approach was developed with the recognition that some patients with complete clinical responses to chemotherapy and radiotherapy may not benefit or

require surgery.

The treatment of colorectal cancer, in general, has been improved through the use of molecular biomarkers and targeted therapies, and in metastatic colorectal cancer, a small percent of patients have tumors which are mismatched repair deficient or MSI-high, and for these patients, the initial use of immunotherapy improves outcome compared to chemotherapy.

Given the benefit of immunotherapy in metastatic colorectal cancer patients with deficient mismatch repair tumors, a natural next step was to evaluate it in the locally advanced setting for patients with deficient mismatch repair rectal cancer, and that was the foundation for the initial dostarlimab experience in deficient mismatch repair stage II/III rectal cancer, and the results in that initial single-arm experience were very provocative, albeit in a relatively small group of patients. Essentially, all patients had complete clinical responses and could potentially avoid surgery. There may even be some patients

with deficient mismatch repair, locally advanced rectal cancer who are cured, as we've heard, or can have long-term, disease-free survival without surgery.

That is what is so exciting to practicing oncologists and patients alike about the proposed GSK phase 2 study design to further evaluate dostarlimab in a larger group of patients with MSI-high deficient mismatch repair, locally advanced rectal cancer across multiple sites. This study has the potential to confirm the benefit of this therapy in a larger group of patients and across a number of different types of practices.

The data from the initial single-arm trial were so provocative that patients are asking about this therapy outside of a clinical trial. Providers also feel this is a very promising therapy, and may be more than tempted to treat with immunotherapy outside of a clinical trial, and this is all the more likely, with observations in multiple diseases, that chemotherapy may be less effective in MSI-high tumors.

Thus, the proposed single-arm, phase 2 study is appropriate and reasonable and I think important to move forward. While a randomized design against the historical standard of chemoradiotherapy and/or chemo would be another option, given the excitement in the colorectal cancer patient and provider community regarding the already seen benefit from the pilot study, a randomized design would be very challenging. It's very likely that patients would enroll, and if randomized to standard therapy, drop out to pursue immunotherapy outside of a clinical trial, or providers would be tempted to treat with other immunotherapy outside of a study. Given the toxicities of chemotherapy and radiotherapy, it would be extremely challenging for patients and providers to accept a randomization between chemoradiotherapy and immunotherapy.

The selection of community sites is an important aspect of the trial design to document the generalizability of this approach and findings across practice sites. The majority of cancer care in the U.S. is conducted at community oncology

practices, and the testing for mismatch repair is quite standardized, and local results for mismatch repair testing have been acceptable in U.S. NCI trials evaluating immunotherapy in deficient mismatch repair colorectal cancer.

Thus, as a practicing GI oncologist for 20 years, and now with a large community practice, I strongly support the GSK phase 2 design of this trial to evaluate dostarlimab in locally advanced, deficient mismatch repair, MSI-high rectal cancer. If this trial confirms the benefit of this agent in this patient population in terms of high, complete, and, importantly, durable clinical response rates, it will certainly change the paradigm for treatment of this challenging disease and potentially spare many patients the toxicities of chemotherapy, radiotherapy, and even surgery, while offering the promise for long-term survival. Thank you very much for your attention and the opportunity to present.

Clarifying Questions to Presenters (continued)

DR. GARCIA: Thank you.

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

We will now take remaining clarifying questions for all the presenters thus far. Please use the raise-hand icon to indicate that you have a question, and remember to put your hand down after you have asked your question. Please also remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

As a gentle reminder, it would be helpful to acknowledge the end of your question with a thank you, and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

DR. ABDULLAH: Dr. Garcia, it's Hesham Abdullah from GSK. I was wondering if I can be recognized just to follow up on some questions before the break, if that's ok.

DR. GARCIA: Absolutely, Dr. Abdullah. Thank you, and yes, please address Dr. Pazdur's questions and comments.

DR. ABDULLAH: Thank you.

Hesham Abdullah, global head of oncology development at GSK. I just wanted to maybe provide some important information that's probably relevant for the committee and the panel members to consider, and maybe just to get at a couple of questions that Dr. Pazdur had raised.

One specifically relates to the ability to be able to conduct the randomized-controlled study in colon cancer, and then the second, really, is very much interrelated in terms of being able to provide confirmatory evidence for an accelerated approval that is potentially considered, or if granted, based on the rectal cancer single-arm data.

I'll start out first by highlighting, of course, GSK's continued commitment and respect of the accelerated approval regulations and, of course, the confirmation of benefit in that regard

as well, too. So with that in mind, I would like to highlight, of course, that both the single-arm rectal cancer study, as well as the randomized colon cancer study, would be done and conducted in parallel, not in sequence. That is an important clarification that I think we need to highlight and consider.

Specifically, the rectal study, which is the GSK sponsored phase 2 trial, would start recruitment in March of 2023, so in just about a month, and the colon study, the randomized-controlled phase 3 trial, would actually start recruitment in June of 2023. So as you can probably tell, both of them will be run in parallel and conducted through parallel tracks.

With that in mind, we're anticipating, of course, data to emerge from the rectal study's primary analysis for cCR12 in q1 of 2026; so that's about maybe 32 months or so from when the first patient is enrolled. And by that time, we anticipate that the last patient in the colon study will have received their first dose. I would

probably say that the majority of patients in the colon study, by the time that the rectal study reads out its primary endpoint, will have already gone through surgery. So I think that is another important clarification to make.

With that in mind as well, too, I think it's probably something that we can think about, consider, and probably have a discussion with the FDA around; that once the data from the single-arm rectal study, which will of course be pooled from across both the MSK and the GSK sponsored trials, are being considered for regulatory decision making, we can certainly look at the data from the colon study and its level of maturity to assess whether or not it would be appropriate in terms of timing to consider potentially interim data analyses or looks.

But again, of course that'll be certainly dependent on where we're at with treatment of patients, follow-up, and of course, the maturity of the results, and that is something that we're very happy to address with the FDA as well, too.

So I think probably one of the things that I'd just like to conclude with is, really, what's important for us to remember? Why are we here? Well, I would say that first and foremost, we're here to really discuss what is a potential path forward based on what are the preliminary data that are being generated from the MSK trial. They're certainly intriguing, yes, preliminary, but very striking given the magnitude of effect, which is important to highlight.

Second, we're looking at a biomarker-defined population in rectal cancer that is an orphan population, as you've heard from some of the prevalence numbers quoted by Dr. Cercek. And then, third, I would certainly highlight, of course, the continued unmet need given the current standard of care, which, based on some of the data Dr. Smith presented earlier in the presentation, is looking at possibly from the OPRA study what is a 35 percent clinical complete response rate in these rectal cancer patients.

So we're looking for a large magnitude of

effect here in the single-arm rectal study, and I'd like to maybe call on Dr. Smith to maybe just comment on the benchmark of 35 percent for clinical complete response rate from the OPRA trial, and his experience in that regard as well, too.

DR. SMITH: This is Dr. Smith. I'd like to just comment on some of the numbers that were shown earlier in the presentation. Remember in OPRA that the patients who had a clinical complete response and near complete response were given the opportunity for organ preservation, so the mature data, we're able to demonstrate what's called TME-free survival in that paper and in that presentation.

In my presentation earlier, we were looking at patients who had a clinical complete response compared to near complete response. These are patients who, if you look in the OPRA data, this was about 38 percent of that group. This is clinical complete response. These are the patients who had the best disease-free survival at 84 percent. So this is where we make a very

conservative estimate of those patients who would have a clinical complete response based on the data that we have from OPRA.

DR. GARCIA: Thank you.

DR. KLUETZ: This is the FDA as well, but let's see if Dr. Pazdur has a response.

DR. GARCIA: FDA, if you want to make a comment or a question? Please proceed as well with Dr. Pazdur.

DR. KLUETZ: Yes. Thank you, Dr. Garcia.

This is Paul Kluetz from the FDA, and I just wanted to provide just one brief comment on context because it's a very complicated space, so I want to summarize a little bit.

The benefit of non-operative management is reduced morbidity of surgery, as we've heard, but the risk is progressing to inoperable or metastatic disease. We've heard that the field has accepted that the risk-benefit for a non-operative approach is acceptable in some cases for patients who achieve a clinical CR and in a select set of treatment settings with multidisciplinary

expertise.

When we were talking about the endpoints, I want people to think a little bit about the difference here between the response rate we're talking about in this setting and the response rate we often talk about at ODAC because we do a lot of metastatic settings. Clinical CR is very different than objective response rate in the metastatic setting. Here, clinical CR has some meaning in and of itself. It's, in this setting, the objective trigger to non-operative management, and the subsequent delay, and avoidance of surgery, and its complications. So I wanted to make sure that we looked at this endpoint differently than we do, for instance, with objective response rate in the metastatic setting.

But again, the risk is missing the opportunity for cure and progressing to inoperable and metastatic disease. So these longer term endpoints, DFS and OS, are intended for us to gauge that risk of progression to inoperative, or metastatic disease, or inferior survival, and as

has been mentioned, the challenge in interpreting these 3- and 5-year endpoints is we don't have a benchmark, particularly in this biomarker-defined population.

So I hope that this context helps a little bit as we discuss the next four discussion points, and that ends my comment.

DR. GARCIA: Thank you, Dr. Kluetz.

Maybe I can just pick up on that comment.

DR. VLAHOVIC: Dr. Garcia, Gordana Vlahovic here from GSK. Do you mind if I add a few more thoughts to what we just heard?

DR. GARCIA: No, please go ahead, and I can ask my question later.

DR. VLAHOVIC: Sure.

DR. GARCIA: Go ahead.

DR. VLAHOVIC: First of all, do you mind if you can switch the slides? Thank you. I would like to share a slide with you while I'm speaking here.

Yes, indeed, clinical complete response is different from ORR, which is in the metastatic

setting; however, in our design, and in the design of MSK, we also have patients called and surveilled very closely throughout the duration of the study, which is 5 years. And if there is any sign of a disease regrowth, tumor regrowth, patients will be treated with standard of care, which includes chemoradiation and, if necessary, surgery.

We know from the prior experience that Dr. Smith has spoken to today that those patients do as well as the patients who receive their treatment upfront, and very importantly, even if disease regrowth happens later, at 2 years, there is also organ preservation and quality-of-life preservation that lasts for 2 years. But overall, when it comes to the risk to the early stage, we believe that the way the study is designed and our careful monitoring of the study, we'll definitely be addressing that concern. Thank you.

More so, there is a small beta, a small cohort, of the dMMR rectal cancer patients who were treated with neoadjuvant chemoradiation, and actually the complete response rate from that

cohort is about 27.6 percent, as you can see on the slide, so that gives us some kind of a benchmark. With us choosing actually 35 percent, the clinical complete response as the benchmark from standard of care, it's rather conservative compared to what we have seen from the dMMR population. Thank you.

DR. GARCIA: Thank you.

Just to expand on Dr. Kluetz -- this is Jorge Garcia -- it's hard for me to avoid thinking as to how do we define surrogacy in cancer and when we do drug development. I don't know if it's semantics or it's just actually the lack of statistical data to support the cCR12.

Everybody has been talking here about a cCR12 as reasonably likely to predict OS, which is a hard point for me to understand. So maybe I can gauge the FDA and also GSK and their stats team in how do you define surrogacy, and have we really actually defined surrogacy where you follow Prentice criteria or something else? Could you both independently speak to that cCR as a true surrogate marker for outcome improvement?

DR. KLUETZ: This is Paul Kluetz from the FDA, if I can begin, Dr. Garcia?

DR. GARCIA: Please, Dr. Kluetz.

DR. KLUETZ: So we've been thinking about the tumor-based endpoints more as intermediate clinical endpoints than surrogates, especially in this case where, as I said, it has meaningfulness in and of itself in that it essentially is the gateway to a clinical intervention that is a de-escalation and has the benefit of decreased morbidity and subsequent, potentially, even mortality for some of these major surgeries.

So in this setting, we would be thinking of this as more of an intermediate clinical endpoint, but as I said, the risk here is the waiting for so long that you may have an incurable scenario by the time you catch it, and that's an important risk, particularly for these younger patients, and really any patient. And how we capture that is going to, unfortunately, be a 3- and 5-year longer term endpoint for which we have no concurrent control, and I think the endpoint discussion is going to end

up probably in how are we going to really evaluate 3- and 5-year OS or EFS in a setting where it seemed that a randomized trial, if not infeasible, will be challenging to conduct.

DR. PAZDUR: If I could just follow up on what Paul mentioned, I think we have to realize that all clinical CRs may not be the same, and this has to be analyzed. Is a clinical complete response rate from chemoradiation the same thing as a clinical complete response rate from an immunotherapy not having radiation therapy? So I think you have some discussion on that because they may not be the same thing, and I think that is an important point.

I don't think we could say that these are true surrogates at this time with our limited information, specifically with the immunotherapy at hand since they really don't have any in this disease, a long-term follow-up, so there are some problems. And here again, I'm focusing not on all of rectal cancer but on the CRs that come from immunotherapy, this PD-1 inhibitor, and its

relationship to long-term outcomes. But I think one has to make a distinction between a CR. Is that from chemoradiation therapy? Does that have the same meaningfulness? And it may be actually better -- I don't know -- from immunotherapy.

DR. GARCIA: Thanks.

DR. VLAHOVIC: Gordana Vlahovic here again. I would like to just address what I just heard about the risk and wait. Just to make clear to everyone, we are not going to be waiting. Patients will be enrolled in the study, and those patients who have any signs, as we are restaging patients and monitoring patients, any signs -- clinical, radiographic -- of disease progression will be immediately treated, switched and be treated with chemotherapy radiation, and surgery, if necessary. Now also, the same path is going to be for the patient that achieves clinical complete response and if they have any tumor regrowth.

Now again, going back to the data that does exist that I'm going to invite Dr. Smith to speak, all the patients that actually had regrowth were

subsequently treated with TNT radiation, and their long-term outcomes were similar to the patients' outcomes who have been having that treatment, standard-of-care treatment, upfront.

Dr. Smith, would you please just come to the podium and say a few?

DR. SMITH: Hi. It's Dr. Smith again. I'll just rehash the data from OPRA, and then also from our own retrospective data from MSK, that patients who had to undergo salvage TME, that we were able to perform the same surgical technique that we have done at the beginning should they have gone to TME after the completion of therapy.

In addition, I would just like to call attention to the point that patients who have clinical complete response -- this is the point about surrogacy of outcome, but we do have data showing that in clinical complete response, there is an association with disease-free survival in OPRA data that I alluded to earlier. And I'll also just call your attention back to the German trial, where they looked at pathologic complete response

and its association with disease-free survival, and these are mature data out of randomized studies.

So I think this is something we cannot overlook. I'm sure you could point back to retrospective data and say there are all the limitations there, but we do have data from prospective studies showing a very strong correlation with response and very important oncologic outcomes.

DR. GARCIA: Thank you.

Dr. Nieva?

DR. CERCEK: Sorry. This is Andrea Cercek; if I can just add just a little bit of further thoughts on this question.

DR. GARCIA: Sure. Go ahead.

DR. CERCEK: With regard specifically to a cCR as we know it, which is achieved with chemotherapy and chemoradiation, and whether this cCR now with dostarlimab alone is equivalent, I think as best as we can tell with the criteria utilized to assess a clinical complete response, the tumor has completely disappeared by endoscopic

exam biopsy, as well as by MRI, and thus the cCR appears to be the same.

Importantly also, we're talking about two cCRs here. One is at the completion of 6 months of therapy, and then the cCR12 is actually after 12 months after the achievement of the first cCR. And during that time period, the patients are followed very closely every 4 months to ensure that they are sustaining their cCR that they achieved after treatment.

DR. GARCIA: Thank you, Dr. Cercek.

DR. FASHOYIN-AJE: Dr. Garcia, this is Lola Fashoyin-Aje from the FDA. May I make a comment, please?

DR. GARCIA: Please, go ahead, Dr. Fashoyin-Aje.

DR. FASHOYIN-AJE: I just wanted to, again, come back to my previous comment about really making sure that we are all on the same page about how we are interpreting the available data that we have.

This notion that we have established a

relationship between cCR and DFS I think is one that is not necessarily supported. We have data from several analyses in quite different contexts in terms of the population studied and treatments administered that is based on a responder analysis. So we don't know, really, what the relationship of cCR, lack thereof, is to these longer term outcomes. So I just want to put that on the table here.

One question I do have for GSK is, based upon the description regarding the enthusiasm for the study, whether they foresee any difficulties enrolling more than the proposed 100 patients that they've described. Thank you.

DR. VLAHOVIC: Gordana Vlahovic here. We propose a study with 100 patients, and certainly as we initiate enrollment, we will keep monitoring to deliver on all the necessary -- the subpopulations that we are hoping, or trying, or we will do our best to deliver in the meaningful numbers so we can assess the benefit.

Would you please clarify the questions?

Were you asking would we be enrolling more than 100 patients?

DR. FASHOYIN-AJE: No. This is Lola Fashoyin-Aje again. I am certain of what your proposal is, which is to enroll 100 patients.

DR. VLAHOVIC: Yes, sure.

DR. FASHOYIN-AJE: I am asking whether you anticipate having difficulty enrolling more than 100 patients onto this trial, because I think we are really operating here in a data-free zone for the most part. I mean, we have these preliminary efficacy results, but we don't really know the natural history of this particular population. We don't know whether we would expect recurrences to take longer to recur, or we don't have a lot of information about subgroups within this heterogeneous population.

So what I'm asking is, what are your thoughts about the feasibility of enrolling more than 100 patients?

DR. VLAHOVIC: We believe that we, actually, with 100 patients, can answer our question. We

believe that 100 patients will provide us with a precision in that confidence interval regarding when we benchmark to 35 percent that we can actually see the treatment effect that is approximately doubled.

For instance, just as an example, 65 percent being the lower bound, from that perspective, we actually believe that 100 patients will be sufficient to provide us with the information and confidence that those dMMR/MSI-high populations in locally advanced rectal cancer do benefit from dostarlimab.

DR LEMERY: Hi. This is Steve Lemery. Can I chime in? To follow up on those points, I think we shouldn't be talking here about a benchmark of 35 percent. The reason why we're here is we've seen so far 100 percent complete CR rate, and I think if we see -- we'll put the number of patients aside, but 5 years down the line, the complete clinical response rate is 100 percent, and no patient relapses, and I think everyone's super happy. But at some point that's probably unlikely

to be the real-world situation, so I think we're having some discussion about what decrement in that would be concerning.

Then also looking at something like DFS, there is some paucity on the long-term DFS of standard therapy in patients with mismatched repair deficient rectal cancer. So if we had, in theory, a 100 percent DFS at 5 years, well, I think everyone would probably acknowledge we're done. But from almost a safety perspective, what is the decrement in DFS at 3 years, at 5 years? That would be concerning.

That's some of our points, and to probe further on the number of patients, I talked about T4 earlier, and I think that will be important to have a sufficient number of patients with T4 or N2 or 3 lesions. Even from a safety perspective, could there be a concern that a small number of patients with T4 lesions will perf, which would be a catastrophic event. If that occurs, we want to be able to describe that in labeling of what is the risk of a perf in a patient with a T4 lesion, for

example.

So I think there are a lot of uncertainties here. I think everyone is excited, especially based on the 100 percent, and no one that we know of has relapsed so far. But ultimately, 3 and 5 years down the line, what kind of data package would say, okay, we're comfortable with this data, we're not putting patients at higher risk, and we're not getting increased numbers of distant metastases? Because we are talking about a single-arm trial here, which will increase the uncertainties at the end of the day.

DR. VLAHOVIC: Yes. I wanted to just share DFS3 rates in locally advanced rectal cancer that we have pulled, and I do have Dr. Smith here who can speak to it. But I just wanted to bring it to your attention, at least for DFS3, the benchmarks that we identified on DFS3 in our particular case.

But going back to it again, I would like to remind everyone of the data we are sharing, and yes, there are data from retrospective studies. There is a prospective study, one, OPRA, that we

mentioned today that is very important to note it's coming from the population that is much more heterogeneous than what we are actually targeting in our study. So that's the population of dMMR/NNMRC [ph].

Again, our population is homogeneous in that sense, because it is biologically very similar. It does have a biomarker for which we are selecting, and it has a good history. When we select that disease or when we select patients based on that biomarker, response is susceptibility to immunotherapy even in the metastatic setting.

I would like to remind everyone of patients who are dMMR/MSI-high in the metastatic setting who respond to immunotherapy, to PD-1 inhibitor, have sustained responses, long-term benefits, and have survival in a metastatic setting, where we would expect patients actually to die within one year. So in totality, I would also want to remind that patients with dMMR/MSI high do have less benefit from chemotherapy. So I will here invite Dr. Smith to add on some additional perspectives on these

primary outcomes

DR. SMITH: These data are just shown to demonstrate the disease-free survival rates in relatively recent randomized trials that show that 76 to 70 percent is fairly representative of what you would find in non-selected populations.

DR. VLAHOVIC: Thank you.

Now before we complete our response, I would like to ask Dr. Abdullah also to end on a comment.

DR. ABDULLAH: Hesham Abdullah, GSK.

Dr. Lemery, I just wanted to respond to a couple points that you raised as well, too, in terms of the sample size of the study itself. I mean, certainly from our perspective, we'd be happy to work with you, with the FDA, around how to best make sure that we have a patient population that is certainly representative of key baseline demographics and prognostic variables that is enrolled into the study.

If that means that we might need to go slightly over 100, I think it's something that we can think about, consider, assess, evaluate, and

discuss with you further, and it's something that we can certainly continue to monitor while the study is ongoing and evaluate based on the demographics of the patient population that we are able to recruit just to make sure that we actually recruit certainly a diverse population that is representative of the disease and the various prognostic variables associated with it as well; so thank you.

DR. GARCIA: Thank you.

Maybe we can just allow Dr. Katsoulakis to ask make your comment or ask a question.

Dr. Katsoulakis?

DR. KATSOULAKIS: I know a lot of the discussion, really, for the cCR, as was previously mentioned, is immunotherapy, the same as chemoradiation. The long-term follow-up is really what's missing and is going to be the key to interpret all of this.

I guess data was shown that this study's follow-up is similar to the OPRA study in terms of the rigorous follow-up, and I know in the study

design there's an incomplete response initially. They're tracked, I think, up to 8 weeks, and then if they don't show or they don't come back, I guess they go to chemoradiation. So far, all the participants think they have had an excellent response, but for the OPRA study, I wasn't sure if anybody was aware of how many patients were lost to follow-up.

I do have concerns in the community setting what will happen to the patients that are, "Oh, my stem [indiscernible] looks great, I'm cancer-free, I'm not coming back," because we have encountered patients like that, and in the GU setting, we don't always put patients on active surveillance protocol, and this is a completely different disease. But if they're not going to come back, sometimes we really advocate for a treatment for them as opposed to a program that they're not going to be able to follow.

So if you could comment on that, that would be great. Thank you.

DR. ABDULLAH: If I understand your

question, you're asking what was the dropout rate in OPRA as we followed them after TNT?

DR. KATSOULAKIS: Yes.

DR. ABDULLAH: Okay. All the patients were followed throughout. There was nobody lost to follow-up, so we would anticipate the same thing. I think the distinction here is that I remember in OPRA that we allowed patients who had a near-complete response to then evolve to a clinical complete response. In this study, we are going to be very strict, using the same regression criteria to only include patients who have a clinical complete response.

DR. GARCIA: Thank you all.

DR. FASHOYIN-AJE: Dr. Garcia, this is Lola Fashoyin-Aje from the FDA. May I make a comment and suggestion?

DR. GARCIA: Yes. Perhaps we can take this as the last comment/suggestion so we can move on to our discussion session. So go ahead, please.

DR. FASHOYIN-AJE: Thanks.

Yes, that's exactly what I was going to

suggest. I think we really are very interested to hear from the members of the committee. We are really grateful that GSK and their invited guests are able to share the experience at Memorial Sloan Kettering, but we do want to hear from other members of the committee about their thoughts on the specific topics that we have posed to the committee. Thank you.

Questions to the Committee and Discussion

DR. GARCIA: Thank you. Great introduction to move on.

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

I will now read question number 1.

We're supposed to be finishing a little bit

over 5:30 or so, so maybe what we'll do, just for ODAC committee members, there are four topics for us to actively review and discuss among ourselves. Ideally, we want to take this time to actually have our own conversation rather than fishing back comments and questions to either the applicant and/or the FDA, but rather just to spend the time talking about the subject at hand and also the presentations that we heard today. We have a talented group of people on the committee with GI oncology expertise, so I'm hoping that we can be an active group.

Question number 1, we can probably spend around 15-20 minutes on on each topic, [indiscernible], before we can vote. Question number 1, I'm going to read it.

Discuss the adequacy of the proposed single-arm trials to evaluate the efficacy and safety of dostarlimab, including the long-term benefits and risks of treatment.

Are there any issues or questions about the wording of this question?

(No response.)

DR. GARCIA: If there are no questions or comments concerning the wording of the question, we will now open the question to discussion.

Maybe what I'll do -- alright, we have some hands up.

Dr. Nieva, do you want to lead this discussion?

DR. NIEVA: Sure. Jorge Nieva, USC Norris. I think the finding of effectiveness here is important when we're thinking about the single-arm Study 219369 as the benchmark. I think the benchmark for cCR12 really should not be 35 percent. If we're going to be defining effectiveness with a single-arm study, I think, really, 75-80 percent is really the benchmark that we should be looking at.

I think the other concern I have is that with single-arm data, there are bountiful opportunities for bias to enter in data cleaning, and I think there needs to be great vigilance to prevent these biases from entering into the

clinical trial because we don't have a control arm. There can be biases created in how radiographic findings are interpreted by using, for example, very strict criteria for the definition of persistent disease rather than looser criteria. I really think the radiographic review has to be blinded and independent, and I'm concerned that any training of radiologists could be biased in ways to reduce declarations of less than CR.

I think central review of eligibility, as they're doing with central review of MSI, generally is good for internal validity, but it reduces external validity; and lack of external validity is really the risk we're all concerned about with treatment paradigm. We're worried that rectal cancer patients might be treated with this regimen based on bad MSI assessments or will be treated in centers where the multimodal treatment teams will provide less than ideal follow-up.

So while I think that a single-arm trial here is appropriate based on the extraordinary preliminary data that we have, I do think we need

to build a confirmatory trial that minimizes bias in favor of declaration of CRs, and I think we need to use real-world determination of MSI, and we need to enroll in smaller centers that maybe don't have the multimodal teams. So how all that is executed I think is going to be critical to be sure that we can really believe the results of a single-arm study. Thank you.

DR. GARCIA: Thank you.

Dr. Nieva, maybe I'll just push a bit on your comment. Could you just expand on your thoughts? You talk about maybe building a better trial, a confirmatory trial. What do you mean by that, based upon the challenges that clearly GI oncology experts in the field appear to feel -- or predict, if you will -- that we may not be able to do such a trial in the future?

DR. NIEVA: So to clarify, Jorge, the question is, what do I mean by the trial 2 or trial 3?

DR. GARCIA: Correct, trial 2.

DR. NIEVA: Yes. In trial 2, there are lots

of things that are built into the current design of trial 2 to maximize internal validity and maximize declarations of CR. That could be done through training of radiologists. My concern is that if there are patients who don't achieve a CR on trial, those patients are going to be doubly scrutinized in order to find reasons to declare them ineligible.

So I want to be sure that when we come up with the rate of what the cCR12 rate is, which I actually think is a perfectly appropriate endpoint here, that we're doing this really based on an intent-to-treat analysis as opposed to a refined eligibility population. So I'm not asking that the trial design be fundamentally changed. I'm simply suggesting that we need to have safeguards in place to prevent biases that are going to be prone to overestimate a cCR rate by excluding progressors.

Does that make sense?

DR. GARCIA: Yes. Thank you for that.

Dr. Ciombor?

DR. CIOMBOR: Yes. I just wanted to make a

couple of comments about this discussion point and perhaps from my experience, and to publicly disclose I'm the national PI for a cooperative group trial that is looking at a different immunotherapy regimen in the same patient population, in MSI-high locally advanced rectal cancer.

From that experience, as well as my broader experience as a GI oncologist treating mostly colorectal patients, I completely agree with some of the points that have been made by Dr. Cohen and others that you really cannot do a randomized trial here. As much as we love randomized trials, and that would be the ideal, I think what has been mentioned is completely accurate in the sense that if you are randomizing to current standard of care, these patients will either not enroll on the study, afraid that they will be randomized to that arm, or if they enroll and get randomized to the standard-of-care arm, they will drop out. So you won't actually get that question answered, unfortunately, as much as we would love to see that

comparison.

We've actually experienced that with the design of our trial and input from patient advocates and others. So I think the single-arm trial is kind of what needs to be done. We need more data. We need more long-term follow-up, and done in a a multi-institutional way, not only with this potential trial, but others.

That was one of my first point, but I can come back. There are a lot of hands up, so maybe others wanted to comment as well.

DR. GARCIA: Thank you, Dr. Ciombor.

Dr. Katsoulakis, do you want to comment?

DR. KATSOULAKIS: Sorry. I think that was an error. I apologize.

DR. GARCIA: Okay. Great.

Dr. Chang, then?

DR. CHANG: Great. Thank you so much. I want to just comment on the question about the adequacy of a proposed single-arm trial, and simply say that given the response rate that we've seen in the dostarlimab study that was presented by

Dr. Cercek -- so the study conducted at MSK -- and other data that we see, including data that we published from MD Anderson as well, the rate of response is incredibly high. If it's not 100 percent, it's pretty darn near close to 100 percent. And for a primary endpoint of clinical complete response, it's very hard to see the rationale for a randomized design because there's no other treatment that we have that can achieve a clinical complete response rate even close to that.

So notwithstanding all the great comments made by everybody about whether or not patients could be randomized or not, if there ever were a study where it was appropriate to do a single-arm trial, I think this would be it, because what we're really talking about is exactly the comment that Dr., I think, Nieva made earlier. There will be a 80 percent or higher rate of complete response. If we were to do a power calculation, I don't think you would need very many patients or patients even able to be randomized. So I do think that it's

quite appropriate to address this in a single-arm way. Thank you.

DR. GARCIA: Thank you.

Dr. Conaway?

DR. CONAWAY: Yes. Mark Conaway. I agree with everything that's been said, and I think from a statistical point of view, with the current trial, there's a very impressive response rate, to say the least, but with that, you have to ask are there issues about how participant selection and the treating institution affect that response rate, and I'm concerned that with the single-arm trial, we're going to be asking those same questions at the conclusion of the trial that you could ask now about the current trial.

Don't get me wrong. I understand completely the difficulty in a randomized trial and understand the weight of evidence for this agent, but ideas have been floated here today. You don't have to randomize 1-to-1 if randomization is completely impossible. I've heard the ideas of constructing a control group. You've got 43 sites right now and

100 participants, that means every site is going to do 2 to 3 participants. There will be participants at those sites who can't get on trial, and it seems like they would be a natural control group.

So it just seems like the design has dropped back from a 1-to-1 randomization, which might be infeasible, all the way back to a single-arm trial that might not answer the question, and I'm just advocating for an exploration of some space in between that will help answer some of the questions.

DR. GARCIA: Thank you.

Is your suggestion, Dr. Conaway, to use the screen failures, review of the patients with screen fails, to get onto standard of care as controls?

(No response.)

DR. GARCIA: Dr. Conaway?

(No response.)

DR. GARCIA: Alright. Maybe we'll move to someone else.

Dr. Vasan?

DR. VASAN: Hi. Neil Vasan. To echo

Dr. Nieva's comments about standardization and implementation of cCR, really the implementation, the sponsor had said that this is a stringent, robust biomarker; however, it requires this multimodal team coming together and making this assessment.

So I think that showing some data for standardization of this metric across disease sites from large cancer centers to smaller hospitals will be really critical for thinking about cCR as a biomarker, and I'm somewhat reminded of, I think, some of the discussion that this group has had about path CR and the nature of path CR in other disease contexts and other drugs as a biomarker. Thank you.

DR. GARCIA: Thank you.

Dr. Madan and Dr. Park?

(No response.)

DR. GARCIA: Dr. Madan? You may be mute. Ravi?

(No response.)

DR. GARCIA: I cannot hear him, so maybe

we'll move Dr. Park, and then we'll go back to Dr. Madan.

(No response.)

DR. GARCIA: Maybe we're having some technical glitch as we speak.

Dr. Lieu?

DR. LIEU: Sure. Can you hear me?

DR. GARCIA: Yes. Thank you.

DR. LIEU: I'll skip the line here.

This is Chris Lieu. I'm going to make this relatively short. I agree with everything that's been said in regards to the inability to make this a randomized trial. I think that's been our experience here at University of Colorado as well. I've thought a lot about what the bar is to allow single-arm studies, and if we're talking about a cCR rate that was around 50 percent, somewhere close to what we might be able to achieve with standard of care, I think there it would be inexcusable to not do a randomized trial, but just because these response rates are so incredibly high, I think that's where we're kind of at, at

this point, where this is likely our only option.

The last thing being, this data doesn't exist in a vacuum, and Dr. Chang had mentioned data from MD Anderson. We certainly have data from the NICE [ph] studies that show the power of this type of therapy and the setting, and I think that that data needs to be considered an aggregate.

One might wonder, well then, is it possible that we're just looking at a subset that's just going to do well no matter what? And I think that it's clear, at least the data that's available, that is not the case with our standard therapy. In fact, there's data to potentially the contrary, where our standard therapies may not be as effective. Therefore, that's the reason why I think the study design is appropriate the way it is. Thank you.

DR. GARCIA: Thank you.

Maybe what I'll do, I'll summarize some of the key points for this question number 1, so we can move on to question number 2, since many of us also have been talking about endpoints and the

appropriateness of those endpoints as a bar.

So it appears that we all, or most of us, do agree that it is impractical or maybe impossible to do a randomized trial. One, obviously, as you may have heard from our group from Vanderbilt, Dr. Ciombor [indiscernible], that practically it would be really hard to do but equally important, just by virtue of the high response that was observed in the Sloan Kettering data. We also talked a little bit about the importance of standardization, that endpoint of cCR across sites, and the concerns, again, as to what we'll probably talk again for the four points, which is variability of how people are reviewing cCR.

Again, I think pretty much the group is pretty impressed with the CR rates observed in this specific patient population, so clearly it does appear that for the purposes of this drug in the context of where this drug has been assessed, that it will be impractical to propose a randomized trial.

So let's move on to question 2. I'm going

to read the question. The committee is asked to discuss the adequacy of the proposed clinical endpoints, complete clinical response rate, event-free survival, to characterize and verify the benefit of dostarlimab, including the proposed timing for their analyses.

Are there any comments concerning the wording of the question?

(No response.)

DR. GARCIA: If there are no questions or comments concerning the wording of the question, we will now open the question for the ODAC committee to discuss.

I see Dr. Kunz. Do you want to start?

DR. KUNZ: Yes. I'm sorry for the delay. This is Pam Kunz and happy to talk to this. I agree with prior comments that have been made and just have some suggestions or recommendations for consideration of adding some stringent testing to the endpoint, as was previously suggested.

The one comment is considering adding organ preservation as either a primary or secondary

endpoint as per the international consensus recommendations. I think we also have an opportunity to really evaluate variability in imaging perhaps through [indiscernible] and digital images. I think that this has been raised a number of times, that we may see some heterogeneity, and I think this is really an opportunity for study and should be considered as another perhaps secondary or tertiary endpoint. Thank you.

DR. GARCIA: Thank you, Dr. Kunz.

Let's go back to Dr. Madan.

DR. MADAN: Yes. See if it works this time. Can you hear me?

DR. GARCIA: Yes, we can hear you. Go ahead.

DR. MADAN: Okay, great. Sorry about that.

This actually kind of dovetails with what I was going to say with the first point, and that is really that I just have a little bit of a concern with the 12-month endpoint. I think we all know that the response rates are high, and they're really good, as was just alluded to, but this data

is immature, and I think we still don't know what happens 3 or 4 years down the road, or at least 2 or 3, in an otherwise curable population.

So I understand the need to pick a time and go with it, but I think the follow-up here is going to be the key. That's going to be the ultimate justification to validate whatever shorter-term endpoints are used.

DR. GARCIA: Thank you

Dr. Park?

DR. PARK: Hello? Can you hear me now?

DR. GARCIA: Yes, we can. Please go ahead.

DR. PARK: Yes. I just have a similar comment. I think this endpoint, cCR 12 months, is inadequate. We are taking away known treatments that can cure, when you look at all the other data, and we're kind of extrapolating out to a single-agent modality that has never been -- we haven't seen anything like that.

So I agree. I think we should not base it on that endpoint. If it was a different endpoint that they were saying, maybe some of their

secondary endpoints -- I saw 3-year event-free survival. We had 95 percent, and it's hard to run a single randomized trial, but we'll use that, and then I think maybe we can have a discussion about accelerated approval. But for this early endpoint, based on chemoradiation data, I have a lot of trouble accepting that. Thank you.

DR. GARCIA: Just to push you a bit on your thoughtful comments, cCR12 you think is inadequate as an endpoint. What is the delta of that difference that you're looking for? We heard quite a bit as to what a cCR indicates in the long term with regards to disease-free survival, in fact, given overall survival.

Also, there was a lot of stress on the fact that when people have local recurrences, they still can go on and have salvage approaches, and if you look at the outcome, even with the limited data that we have, that we saw today, or we heard today, it appears that outcome is not different compared to those patients who moved forward with the standard of care.

DR. PARK: Yes. My thoughts on that are this is a phase 2 trial going for accelerated approval. I think to have a more definitive thing, I would definitely talk about randomization, but just for a specific endpoint, because there's just so much uncertainty, and to pack that all down on another uncertain endpoint, we're just heaping uncertainty upon uncertainty.

So I think we have to have just -- as to why we can't use that endpoint, even if we switch it later on, is because, number one, we're not going to do a randomized trial for that. If we did, that may be a little different. But because we're talking about 100 patients, a new paradigm, lots of uncertainty, we have to pick a better endpoint with a very high bar that can maybe break through some of that, grant accelerated approval, and then test that in a randomized fashion. That's just the way I was thinking about that to maybe forego some of the uncertainty we have. We have to have a much higher bar.

DR. MADAN: This is Ravi Madan, and I'd like

to add to that since we both had the same comment, if that's ok.

DR. GARCIA: Sure. Go ahead.

DR. MADAN: I think the other thing is, the data we have that highlights the path to the 12-month endpoint really comes from different therapies, so we don't know that with immunotherapy that that carries the same relevance, and that gets back to the question of are there non-MSI nests that are left behind and what are the clinical outcomes in that situation.

So I think it's encouraging and I'm comfortable using that as a best known at this moment, but it still is not exactly the data that we need to have confidence, 100 percent, in this endpoint. And again, I think we're used, on this committee, to talking about incremental benefits of progression or survival. I mean, this is a curable population, so as has been said many times, the bar needs to be high.

DR. PARK: I agree. Thank you.

DR. GARCIA: Thank you.

DR. Kunz, do you have another comment or question?

DR. KUNZ: No. My apologies. That was left over.

DR. GARCIA: Alright. No worries.

Dr. Nieva?

DR. NIEVA: I think the endpoint here is actually a good one. I don't see waiting out 3 years or 4 years to be something that we necessarily need to do. I think it's a predictive endpoint in that regard. My only concern is that there be some kind of validation that the radiographic reads and endoscopic interpretations are independently scored, and not only scored by a single entity, and I think that's a pretty easy change to make. Thank you.

DR. GARCIA: Thank you.

Dr. Chang?

DR. CHANG: Yes. Thank you. I would agree with Dr. Nieva that this is a good endpoint. There is ample data about the excellent prognosis in patients who achieve a complete response with our

current treatment modalities. Notwithstanding the very good concerns and comments that have been raised about is it the same, if it's immunotherapy versus traditional therapy, I guess we don't quite know that answer right now.

If this were a randomized design where dMMR patients are randomized to conventional treatment versus an immunotherapy-based approach, I would hypothesize that we would have a pretty dramatic difference. We would certainly have a dramatic difference for clinical complete response, but we would also anticipate a pretty dramatic difference in subsequent event-free survival.

So actually in my comment, I actually have a question as well, and procedurally for the FDA. If this is granted accelerated approval based on a clinical complete response rate, will there be subsequent opportunities to then monitor that event-free survival, and that would then result in a modification of that accelerated approval?

It certainly seems that given what we know, achieving clinical complete response will be

expected to be associated with all of the more favorable outcomes that we'll see, and so if we compare the rates of failure with standard treatment versus what we see in patients who are complete responders, I anticipate there would be a pretty large difference there. But the question has to do with, if approval's granted based on this, what mechanisms exist for monitoring that subsequent event-free survival? Thank you very much.

DR. PAZDUR: This is Dr. Pazdur. The event-free survival would have to be determined by an external control because you don't have a control here. So that's why I was pressing the company, and they agreed to perhaps give us more information and develop an external control here. One would hope that given the big effect that we're seeing on this clinical complete response rate, that this would be much greater and obviate some of the problems that we see with using external controls.

DR. FASHOYIN-AJE: This is Lola

Fashoyin-Aje. I'd like to expand on Dr. Pazdur's comment.

I think the approval decision, if it were to come to that, would really be mostly based upon the endpoint here, this clinical complete response rate, and I think any additional data that we collect long term, and the various mechanisms that have been proposed here, may provide some supportive information.

I think we want to know that patients who are recurring aren't having adverse outcomes compared to what would be expected with standard of care, for example, but those data would really be supportive. We don't anticipate that they would result in independent endpoints due to some of the limitations that we discussed earlier.

I think any sort of external control data comes with a lot of concerns that is probably too much to get into in the context of this meeting, so we would have some reservations about the utility and the role that those types of data would have in our assessment of the effectiveness of this

therapy, but it could be something that's better than nothing, so we would certainly take a look at more specific detailed proposals.

DR. GARCIA: Thank you.

I'm going to ask a question to our ODAC panelist, specifically to Dr. Conaway, and while he processes my question, we can go on to another panel member.

Dr. Conaway, we're talking about maybe defining or finding an external control that can be used to contrast the endpoints or the benefits that this therapy may lead to in this specific patient population. From a statistics perspective, I'm wondering what would be the best way to build that external control, and maybe if you can think as to how would you counsel/ask ODAC committee members to think through that design just to see if we can really actually see what is the true delta of that difference, since clearly we won't be able to actually have long-term follow-up data addressing the question as to is a true cCR a true predictor of outcome improvement in the long term.

So while you think of that, maybe I can ask Mr. Majkowski do you have any comments?

MR. MAJKOWSKI: Yes. Thank you. This is Paul Majkowski from New York. I'm sitting as the patient representative, and I just really wanted to circle back. We're discussing endpoints. I just wanted to really circle back on the quality-of-life issues.

So I'm 8 years out. I had standard of care. I went through the whole sequence of everything, and the quality-of-life issues are very real. So as we've been having this discussion, I've been thinking to myself if I had it to do all over again. I guess one of the takeaways that I'm thinking of, again, is really circling back on the quality-of-life issues. I won't try and state that the 12-month cCR -- I would say, "Well, that sounds good to me," because this sounds like such a positive development in terms of addressing the quality-of-life issues, as I understand the regimen and the study, and even if this were to ultimately become a treatment, there's always the fallback of

returning to standard of care if there was not a response evident.

I just wanted to circle back to focus a little bit on that, all the quality-of-life issues and how important that would be, or how important I think that is in trying to move forward.

DR. GARCIA: Thank you for your thoughtful comment.

Dr. Lieu?

DR. LIEU: Yes. This is Chris Lieu. I just want to highlight just one point in regard to cCR12. When you look at the International Watch and Wait Database, there's really promising data of a correlation between cCR and DFS with the MSK data, but when you look at the International Watch and Wait Database, if you're looking at local regrowth, 64 percent diagnosed within 1 year, 88 percent within 2 years, and then distant metastasis only 11 percent within 1 year, and 54 percent within 2 years.

Even though the cCR12 is actually 18 months from the time that somebody enters into the study,

the question is, is that enough time? To echo some of the points made by Dr. Park and Dr. Madan, you're kind of lumping two unknowns at the same time. We assume that cCR is a surrogate for DFS, and potentially even OS, but we don't know that for sure, and we also don't necessarily know the natural history of these patients.

So that's my only concern in regard to cCR12. We make a lot of assumptions, and I think they're going to be right about what that means for our patients, but we don't know that for sure. Then when you look at an external control or utilization of real-world data, I think that that will help clarify some of the natural history of what these patients experience with standard of care that's obviously fraught with all kinds of different biases.

One of the things that I think we should keep in mind is that we assume that these patients are going to have really, really great responses based off our preliminary data in the prior study, along with many of the other studies that have also

been done in this space with immunotherapy. So really, with any type of external control, you just want to make sure that this patient population wasn't all cured with standard-of-care therapy, where the incredible numbers that we're seeing in this group and in the trials that we've seen to date are just what's going to happen with these patients.

I would just make the point again that from what we've seen thus far, there's no data to support the fact that all these patients get cured with standard-of-care therapy, so the comparator here, it will be important to understand that not all these patients are doing great, and some of the data that we're seeing preliminarily is pretty impressive.

DR. GARCIA: Just to expand on your thoughts, Dr. Lieu, I think the bigger question often -- and again, you do these on a daily basis in your GI oncology practice. But if the question right now is, can I actually put someone in a clinical CR that for some may be cure, for some may

not, and still there's a chance for recurrence; but also because of that, you're delaying the time to a morbid intervention that clearly causes significant detriment in quality of life; and if you salvage or rescue those patients with the standard of care, I think the bigger question for me is, if I can delay the time to a morbid approach, and at the end, my outcome, one, appears to be any different than if I had started with a morbid approach from the beginning, would the time of quality of life be important to our patients if it doesn't really change the clinical outcome?

You know what I mean by that?

DR. LIEU: No. Absolutely. If you take the example to the extreme -- let's just say in every single patient, all we're doing is just delaying a time to surgery, that's not necessarily insignificant in terms of quality of life, and I think this is where quality-of-life metrics in a study like this are so critically important because of the morbidity of some of the interventions that we're proposing. Then if you kind of take it

halfway and just say, well maybe half the patients that otherwise would have received surgery and radiation did not receive surgery and radiation, then there's a benefit already there.

I think what we want to make sure of is that you're not delaying patients a curative operation, and then they all have distant metastasis. Again, I do not think that that is the case. There's no evidence to suggest that that's the case, but that's where an endpoint of event-free survival at 3 years becomes so critically important.

So I think it's the marriage of those two things together to show that complete clinical response does lead to this incredible improvement in event-free survival at 3 years. And then, of course, what's happening concurrently here is the confirmatory phase 3 study, which will also partially answer some of these questions.

DR. GARCIA: Thank you.

Dr. Conaway, any thoughts on building external controls?

DR. CONAWAY: Well, it's a hard question for

the few minutes I had to ponder this, but the easy answer is, the natural control would come out of a randomized trial. But if that is not done, then I'm not sure there is an answer to the question of what's the best way to do that?

It sounds like GSK had considered some options for constructing a control group, but no matter what, if you're going to do a single-arm trial, you need something to compare those results to, historical controls, contemporaneous controls, collected in some way with structured data collection. You need to be able to put the study in context. So I don't know if I have specific advice about the best way to do that.

DR. GARCIA: Thank you for your honest opinion. I'm sorry to put you on the spot.

Let me summarize some of the comments and thoughts that the group has had, and if anybody wants to add, please feel free to do so.

It does seem that the theme from the group is we have a need to add additional endpoints into these clinical trials. Dr. Kunz mentioned adding

organ preservation-based endpoints. We also heard the importance of quality-of-life endpoints that really, really are key to really ensure the success of these approaches, as we noted morbidities of standard of care.

Also, some in the group felt that cCR at 12 months was inadequate, but yet the other group of people also felt that it was sufficient by virtue of the high rates that we have seen, at least in the preliminary data, from the Sloan data, which is supported by many other data out there within the international community and also within the United States.

But clearly, the biggest challenge that we all appear to have is the long-term outcome improvement and whether or not you really are leading to outcome improvements with that cCR, and you may be missing some people who are not cured and the potential for local recurrences, and therefore, distant metastasis. Obviously, one-third of our patients with locally advanced rectal cancer still succumb to their disease, so

clearly if it's made in that context.

Did I miss anything else, team?

(No response.)

DR. GARCIA: Alright. Let's move on, then, to question number 3.

Ms. Bhatt, I'm wondering if we can have question number 3 on the screen? Thank you.

This one is a bit hard for me to understand specifically. Maybe I'll ask some advice from the FDA as to how they want us to handle that or specifically what they're asking us to debate or discuss here. And that is, discuss the study population with the stage II and III locally advanced rectal cancer, MMR deficient, MSI-high unstable, for non-operative management approaches.

So if I could just have the FDA to clarify exactly what do you have in mind with this question. Is it the differences between the stage specifically and the differences that we saw in this long data with less than 20 or 22 percent of patients with T2 disease?

DR. FASHOYIN-AJE: Yes. This is Lola

Fashoyin-Aje from FDA. I'm happy to clarify. I think what we are asking the committee to weigh in on is whether or not there are subpopulations within this entity of locally advanced rectal cancer for whom we expect disease recurrence to be higher based upon the degree of invasion, so T4 tumors or the presence of nodal metastases, such that we want to make sure that those patients are adequately represented in the database that is brought forth to FDA for us to render a benefit-risk assessment for the entire locally advanced rectal cancer population.

Does that clarify?

DR. GARCIA: Yes. Thank you.

DR. FASHOYIN-AJE: Thank you.

DR. GARCIA: Are there any comments or questions concerning the wording of this question?

(No response.)

DR. GARCIA: If there are no further comments or questions concerning the wording of the question, we will now open this question for discussion.

DR. FASHOYIN-AJE: I'm sorry, Dr. Garcia. This is Lola Fashoyin-Aje again. Just a quick addition here.

DR. GARCIA: Sure.

DR. FASHOYIN-AJE: I think the other is consideration for patients with Lynch syndrome for whom we know they have a higher risk of having additional or subsequent tumors, and whether or not there's any consideration for whether or not a non-operative management approach would or would not be appropriate. So we just want to hear discussion and your thoughts on that. Thank you.

DR. GARCIA: Great. Thank you.

One of the things that caught my eye was, obviously, the difference between MMR deficient in MSI-high patients between stage II and stage III. And if I heard correctly, it does appear that as you develop more advanced disease -- probably in this case nodal disease -- that genotype changes and goes lower, at least statistically speaking.

So I don't know. For the GI oncology members in the group, what are your thoughts as to

those differences between stage II and stage III when you dissect the data that was presented today? Maybe I'll pick on Dr. Kunz. You can help me start that discussion.

DR. KUNZ: Hi. Sure. It's Pam Kunz; happy to start. I think it's critically important that those data be collected. I guess the question is whether or not the design should allow for or include preplanned subgroup analyses. I think, obviously, if it's not randomized, we can't do stratification factors, but I think evaluating for Lynch syndrome and also including the patients of T4 disease will be important.

I guess the question is how can we ensure that enough patients from the representative groups are included, but that may be difficult. I think it's fine to include both stage II and stage III.

DR. GARCIA: Thank you.

Dr. Ciombor?

DR. CIOMBOR: Yes. I just wanted to make a comment that I think you also have to be careful, especially with the MSI-high disease, in that

sometimes radiographic assessment can overestimate stage. We tend to see that more with colon than probably rectal, and it's also another reason why I think, actually, the colon study will not be as helpful for a host of different reasons -- that being one of them -- to getting the answer here.

But I would take the staging with a grain of salt because sometimes we see these really aggressive, terrible-looking cancers, and they wind up at resection even without neoadjuvant therapy, being actually not as bad. Obviously, that doesn't happen as much in the rectal population, but still a possibility.

DR. GARCIA: Since I know you were also, obviously, quite involved in the development of the cooperative trial that you described earlier, did you guys see the same challenges when you were thinking as to the ideal patient population and how to stratify?

DR. CIOMBOR: No. I think it was pretty straightforward for us as we were thinking about this design just because stage II and III, we

wanted to keep it as inclusive as possible, but also because we didn't really think that there was dramatically different prognoses with stage II versus stage III as opposed to a non-MSI-high rectal cancer. Of course, that was an assumption and a hypothesis, but we felt that stage II and III would be a reasonable group to analyze together after immunotherapy.

DR. GARCIA: Thank you.

Dr. Chang?

DR. CHANG: Thanks. I do think this is a reasonable population, but to more specifically respond to the FDA question, it often can be quite difficult to distinguish between stage II and stage III because lymph node evaluation on the clinical examination, including with high-quality MRI, has much more limited accuracy than what we once thought. There are many other factors that we do look for on the preoperative evaluation that are probably more prognostic, such as the presence of vascular invasion or lateral pelvic lymph node involvement, et cetera.

So I would say that it's certainly appropriate to look at the stage II-III population, and arguably, I could see investigators locally trying to upstage stage I patients so that they could be eligible. Arguably, that's a group of patients who are most easily treated with this kind of an approach, so that would be one thing to consider, is actually including stage I, considering this does not involve radiation or chemotherapy, it is immunotherapy, which does not carry the same level of toxicity as the traditional approaches.

I would say that there's a population of patients, certainly those who have adjacent organ involvement and certainly with MSI-high tumors. We can have very locally advanced tumors. As the comment was made, radiographically, often even after response, we may not see the same level of radiographic response despite the fact that there will be a pathologic complete response, and that's certainly something that's well known about MSI tumors.

What I would say is, especially for those tumors that are quite locally advanced such as T4B disease, one could argue that those patients do stand to benefit the most from an approach that might allow us to avoid or defer the need for surgery. So I would not feel that that's a population that would not be eligible for a study of this kind of design. Thank you.

DR. GARCIA: Thank you, Dr. Chang.

Dr. Vasan?

DR. VASAN: Yes. It just seems like so much of the discussion that we've had so far has been on just the small numbers of patients with this disease. Dr. Cercek had mentioned 2.7 percent based on the New England Journal IHC paper. It just seems like even if there was a randomized trial, trying to parse out some of these differences with T4 and some of these clinical subsets might still be quite challenging just given the overall rarity of this entity.

DR. GARCIA: Thank you.

Dr. Ciombor, do you have an additional

comment? I see your hand up.

(No response.)

DR. GARCIA: I guess no.

If there are no additional comments or questions, it does seem -- does anybody want to comment about the Lynch syndrome question?

Dr. Lieu, I don't know if you have experience with those patients.

DR. LIEU: This is something where I would actually like Dr. Chang to discuss his management as well because sometimes these patients do go on to total colectomy, depending on what's going on, and patients' own individualized risk of developing cancer. In regards to inclusion of that population in this study, I don't personally have any concerns at all, but there are times where these patients do go on to have surgeries, but that's just to prevent future cancers.

George?

(No response.)

DR. GARCIA: Dr. Chang, do you have any comments?

(No response.)

DR. GARCIA: Alright. We'll move on then. Maybe we can piggyback with Dr. Chang if he gets unmated.

It does seem that it's a pretty straightforward discussion. Everybody felt that stage II and III seems to be a reasonable patient population. There were not many red flags to include, or not include, patients with Lynch syndrome. Granted, there may be some surgical considerations for these patients due to the nature of their disease and the possibility of new recurrences within the colon.

The group also felt that it would be difficult to stratify patients based upon staging just by virtue of the single nature of these trials, and clearly we heard strong opinions as to the importance of critically staging these patients not only before treatment, but certainly after they complete therapy due to the variability of what they see objectively and what one may find pathologically.

Let's move forward with question number 4.

DR. CHANG: Dr. Garcia?

DR. GARCIA: Yes? Who's this?

DR. CHANG: This is George Chang.

DR. GARCIA: Okay. Go ahead, George, if you have any comments.

DR. CHANG: Yes. Sorry. The system wasn't unmuting for me. I just wanted to respond to Dr. Lieu's comment and also the specific question about Lynch.

I think what's behind that question is by not resecting, are we increasing the patient's risk for metachronous tumors? Certainly, there are some people who would advocate for a more extended resection, a prophylactic proctocolectomy, if you will, for patients with Lynch. There is actually pretty good data that would suggest that with adequate surveillance, depending upon the individual patient characteristics, actually from a quality adjusted life expectancy perspective, that in many situations, a more limited resection for patients with Lynch syndrome combined with ongoing

surveillance is as good, if not associated with better quality adjusted life expectancy.

So I agree with Dr. Lieu. I would not have a concern about Lynch patients. Obviously, we'll need to undergo ongoing surveillance. The potential quality-of-life benefit, particularly for rectal cancer patients, is even greater, so that would not be a concern. Thank you.

DR. GARCIA: Thank you for those comments.

Yes, I agree. I will predict that that patient population would be one that will be super-super excited to enroll in clinical trials of this nature, just by what you're describing. Thank you.

Ms. Bhatt, if we can move to question number 4.

This one, I think, is probably to me one of the most important topics because there's no doubt that most of us do agree that this agent has efficacy, has safety, but certainly some of the concerns that the entire committee have expressed individually and collectively relate to the

variability of care and how people are going to be staged, how people are going to be followed, and the quality of care. And Dr. Ng eloquently also presented data of what really happens outside major academic centers with high volume for this particular disease.

I'm going to read the question. The question for the committee is for us to discuss the potential impact of the variability in care, expertise, and the like, across multidisciplinary study staff and across study sites on study conduct, and ultimately on outcomes.

Are there any questions or comments concerning the wording of the question?

(No response.)

DR. GARCIA: If there are no questions or comments concerning the wording of the question, we will now open this question for discussion.

Dr. Ciombor?

DR. CIOMBOR: Yes. Can you hear me?

DR. GARCIA: We can.

DR. CIOMBOR: Okay. I'm back. Great.

My thought on this is that while this is certainly a challenge, I think this is the challenge for non-operative management of rectal cancer in general and what we face moving forward. I think there will be disparities and differences in the ability to do that, based on resources and expertise. But I don't think that is a negative for this study. I think, if anything, you'll probably get the best assessment by these sites.

The issue is when you move it, if it becomes a standard of care at some point, or as it's being used off-label, or immunotherapy, in general, being used off-label for this instance, I think that's where you get into trouble. But I don't think that that's a detriment to the study necessarily, though I do agree the surveillance needs to be rigorously done in a very careful ongoing assessment for patients.

DR. GARCIA: Thank you.

I think any of us who claim to have disease expertise in a particular area always continue to believe that complicated cases really need to be

treated by disease experts. And I don't want to sound demeaning to our community in North America, but it is fair to say that probably 65 -- two-thirds of the patients with cancer in the United States are not being treated at large academic centers but right in community sites, and by great doctors as well. But I think that it raises the question for this specific patient population -- which is not that common, for that matter -- of whether or not these patients ultimately would be better cared for by going to a center of excellence with high volume.

Dr. Madan?

DR. MADAN: Yes. Obviously, there are clinical implications here for the patients, and that's a front-of-mind concern for everybody. But beyond that, this again gets back to the whole 12-month clinical CR component. And if there are inconsistencies in how these multidisciplinary assessments are going to be made through the course of the trial, then 12 months might be too early. They might become much more clinically apparent

given the variabilities and the multidisciplinary approach at later time points.

So again, it just highlights to me why I think that even though you want to choose the 12-month clinical CR, the follow-up is really going to have to be strong and rigorous to validate that. Thank you.

DR. GARCIA: Thank you.

Dr. Kunz?

DR. KUNZ: Yes. I agree this is a really important question, however, I think that it's really important to maintain some heterogeneity of the sites in terms of community practices and academic practices, especially because we don't want to limit access to care. We don't want to limit the diversity of our patients. I think instead, as others have already stated, really increasing the rigor of how we both educate and define these criteria, and perhaps that goes to the GSK team really thinking about what types of supports are going to be provided to the study sites to do this. But I think that we need some

real-world elements in this. And then I actually really think that that needs to be part of the study, as I mentioned previously. Thank you.

DR. GARCIA: Dr. Kunz, after hearing you, I cannot avoid thinking of, well, okay, that's great. We do need heterogeneity across America, and it is fair to say that most of our patients really don't want to come even to facilities that have main campuses and/or regional practices. They want to get their care -- they expect sophisticated care, compassionate care, access to the best available treatment, even access to research strategies in community and at regional sites.

But the reality of that is we also know the complexity of delivering their care, and what I'm worried sometimes as I hear you -- and it's not a criticism of your statement; it's just that it makes me wonder if that heterogeneity will ultimately lead to suboptimal outcomes, and can we afford to have suboptimal outcomes in a patient population that, number one, can achieve cure, and number two, that given the opportunity, if you are

a patient and you're told that your outcome is going to be drastically improved if you drive and/or travel to a center of high volume, that most people will actually look and decide in a different way.

DR. KUNZ: Yes. It's a very good point. I think this is really the balancing act that we need to strike with this study. I think it was -- what -- 45 sites are planned, so it's not going to be an unlimited number of sites, and there will be some level of control over that, and perhaps if community sites are selected, there are ones that have conducted clinical research previously. But I think we need to have some ability to demonstrate that this has some real-world applicability, but I think the devil's in the details in terms of determining what these criteria are, how we educate, and how that gets built into the study.

DR. GARCIA: Thank you. I think to your point, I think the JANUS trial, as Dr. Smith so eloquently stated, helps to also provide that

real-world experience and follow-up. I think the bigger question, again, is the timing of when these trials are going to be completed.

Doctor Lieu?

DR. LIEU: I'm just going to completely, obviously, agree with what Dr. Kunz has already said, and just add on to that. I think that this is truly intention to treat, and the guardrails here are really within the protocol. And I'll be honest with you. With non-operative management, I worry more about the coordination of the follow-ups than I necessarily do about the expertise that it takes to do a flex sig and see if there's a scar in biopsy, yet there may be some heterogeneity in terms of how people read MRIs, depending on how frequently a site does that; and then, obviously, reading CT scans is pretty standard across the country.

So with a protocol, I have very little concerns. I always worry in real life about these patients just falling off the surveillance schedule because it is quite intense, but that won't be a

problem in regards to this particular study. Then on top of that, this is essentially where the field is moving, and I think our community sites are having more and more experience with this, so hopefully the care will race to meet this kind of new paradigm that we're having to deal with fairly quickly.

DR. GARCIA: Thank you, Dr. Lieu. I agree. I think that in the protocol, I think most of us will be comfortable the way the trial has been run, and also the sites they're going to be activating and participating in. I think the bigger question comes, again, as a group, is what happens when this agent is out there, after trials, whether it's approved or used off label, and that is, obviously, a concern that one would have.

Dr. Nieva, what are your thoughts? You are in a place where there's this variability in access. Obviously, you have major academic centers, [indiscernible], in southern California to northern California. How do you think this will play in the west coast?

DR. NIEVA: I think the west coast is like any other place, and for me the issue is going to be variability and biomarker testing. And we need to recognize that there is going to be maybe 5, maybe 10 percent of people with rectal cancer who wind up having a false positive MSI assay on the basis of local testing, who are going to receive this therapy, and it's likely to have zero clinical benefit from them because of the biomarker problem.

So I think the biggest harm and the biggest risk from this approach is going to be that because there's going to be variability in the quality of pathology, both IHC and molecular pathology, that we're going to treat some people incorrectly. And I think it's going to be very important in this clinical trial that the magnitude of that harm is quantified so that we understand that part of the risk of using this strategy is going to be that you shouldn't have gotten it in the first place. So I think it's going to be important that trials that get executed really do an analysis of the intent-to-treat population and not simply the final

refined population. Thank you.

DR. GARCIA: Thank you.

Dr. Ciombor?

DR. CIOMBOR: Yes. I think when it comes to MSI testing or MMR, I actually think it's becoming pretty ubiquitous. And I hope this is not my academic bias, but I don't feel like the test is often wrong. I feel like the biggest challenge is getting it done in the first place, especially with rectal cancer biopsies being limited, and tissue, and sometimes having to do repeated biopsies to get invasive disease tested. So I'd be curious to hear if others are having more difficulty with incorrect results, either false negatives or false positives.

DR. GARCIA: Dr. Ciombor, when you talk of limitations of tissue, certainly in malignancies there's a concordance, which is pretty high, between a liquid biopsy, if you will, and that tumor tissue. How do you feel about that limitation of tissue? Do you feel comfortable or do you feel that the variability could also be if you don't have access to material?

DR. CIOMBOR: I think that's the biggest issue, is access to tissue, because in the localized setting, you're not necessarily doing NGS, or liquid biopsies, or other things because often it's just not paid for. So you're really depending on the rectal biopsy, generally speaking, and that can be limited, or it can just be difficult to make the diagnosis. It can look like dysplasia and not invasive disease, so it can be tough to make that diagnosis of MSI-high.

DR. GARCIA: Any of our GI medical oncologists? Can anybody comment as to the variability of biomarker testing and whether or not that's going to be a challenge when this gets rolled out?

DR. CIOMBOR: I will make one more comment before anybody else chimes in, in that the dostarlimab data has been extremely good for PR and for our patients. So many patients now ask about their biomarker status, where they didn't before, so I think the word is getting out that this is important. Obviously, it's not everywhere, but, I

think that we're moving in the right direction at least.

DR. GARCIA: Thank you.

Dr. Nieva, you have an additional comment?

DR. NIEVA: Just remember, there's going to be places that are going to be rural communities where this is still going to be done under IHC conditions by local pathologists. There's going to be variability where this is going to be getting done in very small hospitals. Rural hospitals in particular, the strategy is going to be incredibly popular because then you have this feeling like you don't need to travel to a multidisciplinary center.

So I think that even in the Memorial Sloan Kettering experience, we had recognition that there were some patients where the initial MSI was positive, and then it was not on further testing. So I think there's going to be lots of communities where there's going to be pathologic variability. I think the last paper I looked at on this subject, the AUC is somewhere in the 0.91 range across different assays, which is good, but it really

means that there's going to be some people treated with this that are going to get harmed. Thank you.

DR. GARCIA: Thank you, Dr. Nieva.

So perhaps if I can summarize this question, clearly there are some concerns about variability in the biomarker testing, differences between IHC and molecular path, with the limitations of tissue material from those rectal biopsies. I'm not sure that we have agreed that a lot of people are not doing genomic testing. I haven't seen real-world data, but most people in America with oncologic issues are requesting genomics, but it's possible that, again, depends on where you are. Some people are still not actively engaged in that process.

It seems that there is an expectation that it is important for us to continue seeing heterogeneity, not only in access but also just to document what really would happen in the real world outside of a clinical trial for these patient populations. We also agreed on the importance of education, the importance of how are you going to train the community not only on protocol but in the

future as well, how to define a clinical complete response, and looking at endoscopic evaluations, MRIs, and the like. There clearly appears to be a big difference between protocol life and real life.

If there is no further discussion on this question, we can move on and begin the next question.

We will now move on to question number 5, which is a voting question. Ms. Rhea Bhatt will provide the instructions for the voting.

MS. BHATT: Thank you, Dr. Garcia.

Question 5 is a voting question. Voting members will use the Adobe Connect platform to submit their votes for this meeting. After Dr. Garcia has read the voting question into the record, and all questions and discussion regarding the wording of the vote question are complete, Dr. Garcia will announce that voting will begin.

If you are a voting member, you will be moved to a breakout room. A new display will appear to submit your vote. There will be no discussion in the breakout room. You should select

the radio button, the round circular button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected. Please note that you do not need to submit or send your vote. You only need to select the radio button that corresponds to your vote. You will have the opportunity to change your vote until the vote is announced as closed. Once all voting members have selected their vote, I will announce that the vote is closed.

Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Next, Dr. Garcia will go down the roster, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you wish to.

Are there any questions about the voting process before we begin?

(No response.)

MS. BHATT: If not, we can move on to question 5 for the voting question.

DR. GARCIA: I just lost my screen, but I'm going to do this with the document. I'm going to read the question. This is a voting question.

Will the data from the proposed single-arm trials, enrolling a total of 130 patients, be sufficient to characterize the benefits and risks of dostarlimab in the curative-intent setting for patients with mismatched repair deficient dMMR and microsatellite instability-high locally advanced rectal cancer?

Are they any issues or questions about the wording of this question?

(No response.)

DR. GARCIA: If there are no questions or comments concerning the wording of the question, we will now begin the voting on question 5.

DR. FASHOYIN-AJE: A couple of people have their hands raised.

MS. BHATT: Yes.

DR. GARCIA: Alright. Go ahead.

DR. KUNZ: Hi. It's Pam Kunz.

DR. GARCIA: Someone has a question? Go

ahead, Dr. Kunz.

DR. KUNZ: Great. Thank you.

This is Pam Kunz. I have a question about the question just in terms of does a yes answer imply that we agree with the proposed current endpoints or does it allow for suggested modifications to the endpoint that has been discussed by the committee? Thank you.

DR. GARCIA: Would the FDA like to --

DR. FASHOYIN-AJE: Would you like me to clarify?

DR. GARCIA: That would be great, if you can.

DR. FASHOYIN-AJE: Great. This is Lola Fashoyin-Aje. I think what we're asking you is to really comment on whether the totality of the proposal that we've been discussing is adequate. I think if you find it mostly adequate but there are some areas where you'd like to see changes made, then your vote would be a no. I think we've heard a lot about the single-arm trial design, which seems to be acceptable to most, so there are other

aspects of this question that you may want to specifically comment on. Thank you.

DR. GARCIA: Thank you.

Are there any additional questions or comments related to the wording of this question?

(No response.)

DR. GARCIA: If there are no questions or comments concerning the wording of the question, we will now begin the voting on question 5.

MS. BHATT: We will now move voting members to the voting breakout room to vote. There will be no discussion in the voting breakout room.

(Voting.)

MS. BHATT: You have 15 seconds before the vote closes.

(Pause.)

MS. BHATT: The vote is now closed. We will momentarily return to the main meeting room.

(Pause.)

MS. BHATT: The voting has closed and is now complete. Once the vote results display, I will read the vote results into the record. Dr. Garcia

will go down the list, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you wish to.

There are 8 yeses, 5 noes, and zero abstentions.

(Pause.)

MS. BHATT: Dr. Garcia?

DR. GARCIA: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification for your vote, if you wish to.

We'll start with Dr. Lieu?

DR. LIEU: This is Chris Lieu, and I voted yes. Obviously, in this setting, as has been discussed, I don't think a randomized study is feasible given the presentation of the existing data and patients' overall goals and expectations.

I will clarify, I do have some concerns about the use of complete clinical response at 12 months as the definitive endpoint mainly because

I don't think that there's a clear correlation, although there's a suggestion that there's a correlation between complete clinical response and disease-free survival and distant metastasis rates. That's just my only concern in regards to the complete clinical response rate as a definitive endpoint.

I do think the endpoint of event-free survival at 3 years, which is a secondary endpoint of the study, will be critically important just to show that correlation, but overall, I believe that the study as designed will provide the data needed for accelerated approval. Thank you.

DR. GARCIA: Thank you.

Mr. Mitchell?

MR. MITCHELL: Yes. Thank you. I'm David Mitchell. I voted yes. If the frequency of disease is as small as the discussions today suggested, it's probably difficult, but not impossible, as Dr. Lieu just said, to accrue a randomized standard control arm, even a small one, as one of the public commenters suggested.

Second, given the initial very positive data, I do think it's difficult to get patients to enroll in a control given the irreversible toxicities, and lifestyle, and extreme quality-of-life sacrifices. And finally, accelerated approval is for patients, and this feels like a conditioned and a potentially enormous step up in care for patients that's worth going with the current proposed trial design, not waiting 3 to 5 years.

DR. GARCIA: Thank you, Mr. Mitchell.

Dr. Katsoulakis?

DR. KATSOULAKIS: Hi. Yes. I voted no, just on the fact I wish there were some of the modifications that were discussed during our sense of discussion here, [indiscernible]. I apologize. I was trying to pull up a study we had performed in the VA. There are discordances I see in NGS testing, but we do have ability to sequence many patients, but there is a substantial discordance.

For the biomarker testing, the 3-year event-free survival I think is a more meaningful

mark for these patients, and if we just rely on the 12-month cCR, and then we can't go back on accelerated approval, that might be an issue. And that often is with a lot of the accelerated approvals for the drugs, then a subsequent follow-up that kind of goes by wayside. So I did have some concerns about that, and possibly using this marker in other sites [indiscernible] a defense entity, and what would that mean for the future and the landscape of oncology.

I think this is a a great opportunity. I would have just liked to have seen a little more regulation in terms of the design, but otherwise I hope this drug is promising, and I just wish it had a higher threshold and more of the intention-to-treat kind of discussion that was had earlier. Thank you.

DR. GARCIA: Thank you.

Dr. Chang?

DR. CHANG: Yes. I'm George Chang, and I voted yes. I think Chris Lieu very eloquently made all the comments that I would make. I do think

that monitoring that 3-year event-free survival will be very critical, but given the compelling nature of the current data, I think this warrants moving forward. Thank you.

DR. GARCIA: Thank you.

Dr. Park?

DR. PARK: Yes. I voted no. I think extrapolation from the chemoradiation data to single-agent immunotherapy is a little too early, and I think the cCR endpoint is also inadequate. Those are the main reasons for voting no. Thank you.

DR. GARCIA: Thank you.

I'm Jorge Garcia, and I voted no. I literally voted no because I think the question literally and grammatically was clearly stated, whether or not this data was sufficient, and I don't believe this data is sufficient.

I do believe this agent has great safety, has efficacy, and has a pretty impressive clinical complete response with the current data, and I do believe there's a huge opportunity for us to delay

for some maybe never having to have the morbidity of a surgical chemorad or surgical approach. However, I do not believe the data that we have and the data that has been proposed by the applicant is sufficient to characterize the benefits and risk in the curative-intent setting for this patient population. Thank you.

Dr. Nieva?

DR. NIEVA: Jorge Nieva, USC. I voted yes. Will the data be sufficient? Yes, I think it will. But will the analysis be sufficient? That part I'm not so sure for all the reasons Dr. Katsoulakis stated. There's going to be variability in the biomarker, and we're going to be defining the enrolled population down to the eligible population, and I think potentially misinterpreting the data that we get. We're not going to be liberal in the radiographic definitions of what is persistent disease; we're going to be very strict about that. And because of that, also we make this study less valid to the external world if it's interpreted that way.

So I think the design and the data we get is going to be sufficient, but I do think we need to be very careful in the analysis that's finally done. Thank you.

DR. GARCIA: Thank you.

Dr. Ciombor?

DR. CIOMBOR: Yes. This is Kristen Ciombor. I voted yes. While the proposed studies certainly won't answer all of our questions about the optimal use of immunotherapy in MSI-high locally advanced rectal cancer, I think they'll provide additional data to determine whether the initial pilot results are generalizable given the multi-institutional/ multinational nature of the proposed studies, longer follow-up, and increased sample size. So on that basis, I voted yes.

DR. GARCIA: Thank you.

Dr. Conaway?

DR. CONAWAY: Yes. Mark Conaway. I voted no. Despite the extraordinary promise of the agent and concerns about the feasibility of doing a randomized trial, I voted no because of the

difficulty in interpreting the results of non-comparative trials and the uncertainty around the long-term applicability of the endpoint.

DR. GARCIA: Thank you.

Dr. Vasan?

DR. VASAN: My name is Neil Vasan, and I voted no. Despite the incredible data, the response rate data, and the very compelling patient testimonials, I felt that the data were not sufficient -- again, to sum up what Dr. Garcia said about the word, "sufficient" -- given the nature of the clinical complete response 12 endpoint, especially in this curative setting.

DR. GARCIA: Thank you.

Dr. Kunz?

DR. KUNZ: Hi. This is Pam Kunz. I voted yes for many of the reasons already stated. I believe in the single-arm design, and I'm supportive of cCR as an acceptable primary endpoint. However, I do think that we need to expand on some of the secondary endpoints as has been previously discussed.

The event-free survival is already added, but adding organ preservation rate, considering adding central confirmation, and dMMR/MSI-high as part of the eligibility criteria and quality of life. I really think that our goal -- and appreciate robust conversation from colleagues today but, really, it's this balancing act of identifying effective agents, and minimizing morbidity, and providing access. I think that this trial will really be the first attempt to do that in this disease, so I voted yes. Thank you.

DR. GARCIA: Thank you.

Mr. Majkowski?

MR. MAJKOWSKI: This is Paul Majkowski. I voted yes. I think that, for me, in the context of improvement to quality of life, data and the design is sufficient at this stage to warrant essentially moving on. Again, to collect that data at this stage and move on, I think that it's sufficient, again, viewing that largely in the context of the promise of improving the quality-of-life aspects of treatment of the disease. Thank you.

DR. GARCIA: Thank you.

Dr. Madan?

DR. MADAN: I voted yes, but I think that this planned study in rectal cancer with dostarlimab is suboptimal. That said, I don't think a randomized study will be feasible because, as the discussion highlighted today, PD-1 inhibitors will likely be used off-label, and if off-label use becomes the standard practice, then there will be no way to capture data prospectively. Therefore, that makes this proposed trial important as perhaps the only means to obtain that perspective data.

I'm not a hundred percent confident in the 1-year clinical CR endpoint. That makes transparency an adequate follow-up for durability of response really incumbent upon the sponsor to share with the FDA and the public as it becomes available. Those endpoints must also remain at a high bar for cure rate, and not just survival, in a population that likely would be cured with standard of care. So this trial is a potential platform to

get the data, but the questions must be asked appropriately and rigorously evaluated. Thank you.

DR. GARCIA: Thank you.

Would you mind to restate your name for the record, Dr. Madan?

DR. MADAN: Yes. This is Ravi Madan, and I voted yes.

DR. GARCIA: Thank you.

How can I summarize this vote? The only thing that I can come out with is three single letters, B-U-T, BUT. The group who voted yes believe in the efficacy, believe in the safety, believe in the clinical complete response at 12 months as an adequate endpoint, but everybody pretty much agreed that there were some concerns as to the long-term outcome with this agent.

Everybody, to the extent to what I gathered, felt that the data would be sufficient, but yet again, the analysis of what comes out of that data may not allow us to define the outcomes that we're seeking to achieve. Also, importance was expressed on the secondary and tertiary endpoints and the

importance of quality of life.

For the group who voted no, again, B-U-T, BUT. We took that into consideration, and I think most of us felt that the data, although great with existing data, was not sufficient to demonstrate the outcome that we are seeking as patients.

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

DR. FASHOYIN-AJE: Dr. Garcia, this is Lola Fashoyin-Aje. On behalf of the FDA, I just want to thank the committee for this really excellent discussion. I think more important than the vote was really the discussion that we had throughout the meeting. I also want to thank the Division of Advisory Committee Consultants, the audiovisual staff, our invited guests, Dr. Kimmie Ng, who gave us a masterful review of treatment of rectal cancer; the GSK team for agreeing to participate in this somewhat atypical ODAC; and the members of the FDA clinical, statistical, regulatory teams for their contributions to this meeting.

And thank you, Dr. Garcia, for really doing

a great job at keeping everyone on track with giving us the feedback that we were looking forward to. Thank you.

Adjournment

DR. GARCIA: Thank you, Dr. Fashoyin-Aje, and thanks again to the FDA for their commitment for the guidance today. To the committee members, I appreciate your effort. I appreciate our discussions. Thank you also to GSK, and I echo also the comments as to the outstanding clinical faculty who presented today.

We will now adjourn the meeting. Thank you all very much.

(Whereupon, at 5:22 p.m., the meeting was adjourned.)