FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEDICAL IMAGING DRUGS ADVISORY COMMITTEE MEETING

(MIDAC)

Virtual Meeting

Tuesday, March 5, 2024

9:00 a.m. to 5:05 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

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Office of Executive Programs, CDER, FDA

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

DR. ROYAL: Good morning, and welcome. I would first like to remind everyone to please mute your line when you are not speaking. For the media and press, the FDA press contact is Amanda Hils. Her email is currently displayed. My name is Henry Royal, and I will be chairing this meeting. I will now call the March 5, 2024 Medical Imaging Drugs Advisory Committee meeting to order. Dr. Jessica Seo is the acting designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

DR. SEO: Good morning. My name is Jessica Seo, and I am 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 standing members of the MIDAC, starting with Dr. Applegate.

DR. APPLEGATE: Hello. My name is Kimberly Applegate.

DR. SEO: Thank you.

Next, we have Dr. Bolch.

DR. BOLCH: Yes. This is Wes Bolch, University of Florida, Biomedical Engineering and Medical Physics.

DR. SEO: Thank you.

And Dr. Hackney?

(No response.)

DR. SEO: Dr. Hackney, you might be muted.

(No response.)

DR. SEO: Dr. Hackney, if you can hear me, it looks like you're still muted on Zoom.

(No response.)

DR. SEO: We'll go ahead and continue, and I'll return to Dr. Hackney at the end.

Next is Dr. Jacobs.

DR. JACOBS: Paula Jacobs. I'm with the National Cancer Institute and the Division of Cancer Treatment and Diagnosis, and I'm an expert advisor on medical imaging to the division.

DR. SEO: Thank you.

Next is Dr. Oates.

DR. OATES: Yes. Hi. Liz Oates. I'm at the University of Kentucky in radiology, and also nuclear medicine, molecular imaging, and radiotheranostics.

DR. SEO: Thank you.

Dr. Rosenthal?

DR. ROSENTHAL: Good morning. Eben Rosenthal. I'm at the Vanderbilt University Medical Center. I'm a surgical oncologist with an interest in surgical imaging and molecular imaging.

DR. SEO: Thank you.

And next is Dr. Royal.

DR. ROYAL: Hello again. My name is Henry Royal. I'm a nuclear medicine physician at Washington University in Saint Louis, Missouri.

DR. SEO: Thank you.

And Dr. Xiong?

DR. XIONG: Good morning. Chengjie Xiong is here, and I'm a biostatistician from Washington University in Saint Louis.

DR. SEO: Thank you.

We also have our acting industry

representative, Dr. Bryant.

DR. BRYANT: Good morning. LaMont Bryant, Global Head, Regulatory Affairs, Johnson & Johnson, MedTech Surgery, and also head of GPI in value creation. I'm the industry representative. Thank you.

DR. SEO: Thank you.

Next, we'll introduce our temporary voting members, beginning with Dr. Burstein.

DR. BURSTEIN: Good morning. Hal Burstein, a breast medical oncologist at Dana-Farber Cancer Institute and Professor of Medicine at Harvard Medical School.

DR. SEO: Thank you.

Next is Dr. Dejos.

DR. DEJOS: Hey team. So sorry. I think I had some audio difficulty. My name is Mike Dejos. I'm the Assistant Medication Safety Officer at Methodist Le Bonheur Healthcare in Memphis, Tennessee.

DR. SEO: Thank you, Dr. Dejos.

Next is Dr. Dykewicz.

DR. DYKEWICZ: Good morning. I'm Mark Dykewicz. I'm at Saint Louis University School of Medicine, Saint Louis, Missouri, where I am Chief of Allergy and Immunology, and Professor, Internal Medicine.

DR. SEO: Thank you.

Next we have Ms. Fisher.

MS. FISHER: Hi. Good morning. I'm Melissa Fisher. I am a bilateral IBC patient, advocacy, serving as the patient representative.

DR. SEO: Thank you.

Next is Dr. Greenberger.

DR. GREENBERGER: Good morning, everyone. I'm Paul Greenberger, Division of Allergy and Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine in Chicago.

DR. SEO: Thank you.

Next is Dr. Griffin.

DR. GRIFFIN: Good morning. I'm Marie Griffin. I'm a general internist and epidemiologist, and Professor of Health Policy America at Vanderbilt University.

DR. SEO: Thank you.

And we have Ms. Pearson.

MS. PEARSON: Good morning. I'm Cindy Pearson. I'm the consumer representative, acting consumer representative.

DR. SEO: Thank you.

Next is Dr. Richardson.

DR. RICHARDSON: Good morning. I'm Andrea Richardson. I'm Professor of Pathology and Oncology at Johns Hopkins and Director of Pathology for the National Capital Region for Johns Hopkins Medicine.

DR. SEO: Thank you.

Next is Dr. Skates.

DR. SKATES: Good morning. I'm an early detection researcher at Massachusetts General Hospital and Harvard Medical School, with a background in biostatistics, and I'm also at the MGH Cancer Center.

DR. SEO: Thank you.

And Dr. Vasan?

DR. VASAN: Good morning. I'm Neil Vasan,

and I'm an assistant professor of medicine at Columbia University. I'm a breast oncologist and also a laboratory-based physician scientist.

DR. SEO: Thank you, and I'll take this moment to return to Dr. Hackney.

Dr. Hackney, if you'd like to turn on your webcam and unmute, and introduce yourself for the record, please?

DR. HACKNEY: Hi. I'm David Hackney. I'm a neuroradiologist at Beth Israel Deaconess Medical Center in Boston and Professor of Radiology at Harvard Medical School.

DR. SEO: Thank you, Dr. Hackney.

We will now introduce our FDA participants, beginning with Dr. Ganley.

DR. GANLEY: Hello. I'm Charlie Ganley. I'm the Director of Office of Specialty Medicine.

DR. SEO: Thank you.

Next is Dr. Gorovets.

DR. GOROVETS: Hi. This is Alex Gorovets. I'm Deputy Director, Office of Specialty Medicine, Office of New Drugs, CDER. Thank you.

DR. SEO: Thank you.

And we have Dr. Marzella.

DR. MARZELLA: Good morning, all. I'm Lou Marzella, and I'm the Director of the Division of Imaging and Radiation Medicine in CDER at FDA.

DR. SEO: Thank you.

Next is Dr. Hofling.

DR. HOFLING: Hello. I'm Alex Hofling. I'm the Deputy Director of the Division of Imaging and Radiation Medicine, CDER, FDA.

DR. SEO: Thank you.

Next, we have Dr. Rajpal.

DR. RAJPAL: Hi. I'm Anil Rajpal, Deputy Director for Safety in the Division of Imaging and Radiation Medicine.

DR. SEO: Thank you.

Next is Dr. Masters.

DR. MASTERS: Hello. I'm Shane Masters. I'm a clinical team lead in the Division of Imaging and Radiation Medicine.

DR. SEO: Thank you.

And Dr. Wang?

DR. WANG: Good morning. My name is Sue-Jane Wang, the Deputy Director of Division of Biometrics I, Office of Biostatistics and Office of Translational Sciences at CDER, FDA.

DR. SEO: Thank you.

Next is Dr. Paterniti.

DR. PATERNITI: Good morning. Miya Paterniti, Clinical Team Leader for the Division of Pulmonology, Allergy, and Critical Care.

DR. SEO: Thank you.

Next is Dr. Bean.

DR. BEAN: Good morning. I'm Rachel Bean, the clinical reviewer in the Division of Pulmonology, Allergy, and Critical Care.

DR. SEO: Thank you.

And we have Dr. Bird.

DR. BIRD: Steven Bird, Division of Epidemiology, FDA.

DR. SEO: Thank you.

Next is Dr. Gelperin.

DR. GELPERIN: Good morning. Kate Gelperin. I'm a medical officer in the Division of

Epidemiology and Office of Pharmacovigilance and Epidemiology.

DR. SEO: Thank you.

Next is Dr. Mundkur.

(No response.)

DR. SEO: Dr. Mundkur, if you're available, please introduce yourself.

(No response.)

DR. SEO: I apologize. I don't believe we're able to hear. Dr. Mundkur has not arrived yet, so we'll return to her when she arrives.

We'll move on to Dr. LaCivita.

DR. LaCivita: Good morning. My name is Cynthia LaCivita. I'm the Director for the Division of Risk Management in the Office of Surveillance and Epidemiology, CDER at FDA.

DR. SEO: Thank you.

And Dr. Carr?

DR. CARR: Good morning. Jessica Carr, Assistant Director of the Cancer Diagnosis and Treatment Devices Team, CDRH at FDA.

DR. SEO: Thank you.

Next is Dr. Korz.

DR. KORZ: Good morning. Dorian Korz, Chief Medical Officer at the Office of Surgical and Infection Control Devices and the Center of Devices in Radiological Health.

DR. SEO: Thank you.

And we have Dr. Chen.

DR. CHEN: Good morning. My name is Colin Kejing Chen. I'm a team leader for the Cancer Diagnostics and Treatment Devices Team at CDRH.

DR. SEO: Thank you.

And finally, Dr. Nagel.

DR. NAGEL: Steven Nagel, FDA Medical Officer, CDRH.

DR. SEO: Thank you.

I'll now return the floor to you, Dr. Royal.

DR. ROYAL: 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 be a fair and open forum for discussion of these issues, and that individuals can express their views

without interruption. As a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

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

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

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

DR. SEO: Thank you, Dr. Royal.

Before I read the Conflict of Interest Statement, I apologize. It was brought to my attention I did not ask Dr. Leitch to introduce

herself. I skipped over her, and I, again, really apologize for that.

Dr. Leitch, would you please go ahead and introduce yourself for the record?

DR. LEITCH: Hello. I'm Marilyn Leitch, a surgical oncologist and Professor of Surgery at UT Southwestern in Dallas, Texas. My practice is focused primarily on breast cancer.

Conflict of Interest Statement

DR. SEO: Thank you so much, Dr. Leitch, and again, my apologies.

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

The following information on the status of

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

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

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential

financial conflicts of interests of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussion of efficacy and safety data submitted in support of new drug application, or NDA, 214511, for pegulicianine for injection, the optical imaging drug constituent of a drug device combination product submitted by Lumicell, Incorporated. The proposed indication for pegulicianine is for use in adults with breast cancer as an adjunct for the intraoperative detection of cancerous tissue within the resection cavity following removal of the primary specimen during lumpectomy surgery.

This is a particular matters meeting during which specific matters related to Lumicell's NDA will be discussed. Based on the agenda for today's

meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

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

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such

involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committees of any financial relationships that they may have with the firm at issue.

Thank you, and I'll hand it back to you Dr. Royal.

DR. ROYAL: We will now proceed with the FDA introductory remarks from Dr. Alex Hofling.

FDA Introductory Remarks - Alex Hofling

DR. HOFLING: Hello. I'm Alex Hofling, Deputy Director of the Division of Imaging and Radiation Medicine in the Office of Specialty Medicine, Office of New Drugs, CDER, FDA. I'd like to welcome everyone to today's Medical Imaging Drugs Advisory Committee meeting. Here's an outline of FDA introductory comments. I'll begin with an overview of the product that we'll be discussing today and the purpose of today's meeting.

A goal of my talk is also to touch on some of the unique regulations, guidance, and precedent

that set imaging drugs apart from the much larger group of therapeutic drugs. As such, I'll discuss some points from FDA guidance for general imaging drug development, with particular focus on indications, trial design, and efficacy endpoints. I will then briefly touch on considerations that are more specific to optical imaging drugs and present an example of an approved optical imaging drug. Then I'll conclude with introduction of the questions and discussion points for the advisory committee.

Pegulicianine, trade name Lumisight, is the direct constituent of a combination product that includes the Lumisight direct visualization system device. The established pharmacologic class of Lumisight is an optical imaging agent. Lumicell, the applicant, has submitted an NDA for the indications of fluorescence imaging in adults with breast cancer as an adjunct for the intraoperative detection of cancerous tissue within the resection cavity following removal of the primary specimen during lumpectomy surgery. As will be discussed

further in my talk, this is a disease detection type of imaging indication.

I would like to briefly touch on the regulatory classification of the Lumisight optical imaging agent. Recent legislation has clarified that imaging agents historically regulated as drugs are now indeed defined as drugs by law. Specifically, Section 3621 of the Consolidated Appropriations Act of 2023 states that any contrast agent shall be deemed to be a drug and not a device, where the term "contrast agent" means an article that is intended for use in conjunction with a medical imaging device, and is either a diagnostic radiopharmaceutical or is a diagnostic agent that improves the visualization of structure or function within the body by increasing the relative difference in signal intensity within the target tissue, structure, or fluid. Optical imaging agents like Lumisight are included in the latter of these two groups of contrast agents and are therefore defined and regulated as drugs.

For drug approval, FDA requires evidence

that a drug's benefit to patients outweighs its risks. This requirement is what brings us here today at this advisory committee meeting to discuss evidence of effectiveness of Lumisight; to discuss safety risk related to adverse reactions; and to weigh these two elements to determine favorable or unfavorable balance.

Moving now to FDA guidance for development of imaging drugs, we will begin by looking at common types of indications. These include structure delineation indications such as visualization of lesions with abnormal vascularity by gadolinium-based contrast; functional, physiological, or biochemical assessment indications such as estimation of glomerular filtration rate by Technetium-99m pentetate; disease or pathology detection or assessment indications such as detection of bladder cancer lesions by hexaminolevulinate hydrochloride; and diagnostic or therapeutic management indications such as selection of patients with prostate cancer for targeted radioligand therapy by gallium-68

gozetotide.

Of note, this list of indications is not meant to be exhaustive, and to date, most imaging drugs, including optical imaging drugs, have been approved for structure delineation indications, or disease or pathology detection, or assessment indications. The proposed indication for Lumisight is in the disease or pathology detection or assessment class, hereafter referred to as a disease detection indication for simplicity.

To determine effectiveness of imaging drugs, FDA guidance states that one should establish accuracy or validity of imaging performance, as well as the clinical value or usefulness of the drug. In the coming slides, we will focus on these requirements in a specific context of indications for disease detection.

Beginning with accuracy or validity, or what will be referred to hereafter as diagnostic performance, clinical outcome data are typically not required to support a disease detection indication; instead, imaging results are compared

against a reference or truth standard. A reference standard is an independent method of measuring the same variable measured by the investigational drug and to closely approximate the true measurement of this variable. Of note, it may not be feasible for a reference standard to perfectly reflect truth.

Continuing with the concept of a reference standard, histopathology is typically favored for determining the presence of a disease or pathology, but it can be sometimes difficult to collect at all, never mind in a systematic fashion. It may be acceptable to use other reference standards for a disease detection indication, including follow-up clinical information and conventional imaging.

In terms of endpoints for establishing diagnostic performance for a disease detection indication, sensitivity and specificity are typically preferred but require reference standard information to be collected systematically to characterize all events as either true positive, true negative, false positive, or false negative.

As mentioned previously, such systematic

collection of reference standard information that allows calculation of sensitivity and specificity may not always be feasible, particularly in optical imaging drug trials. For example, complete assessment of false negative and true negative results is often challenging in these trials.

The trials conducted to support Lumisight approval actually did capture reference standard information systematically and enabled calculation of sensitivity and specificity, thereby allowing determination of whether test performance is better than chance. Of note, depending on the clinical context, lower sensitivity or specificity, even below 50 percent, might be balanced by a higher value of the other metric. Aside from sensitivity and specificity, other imaging performance endpoints that can support a disease detection indication include disease detection rate and false positive rate, and these are commonly used in optical imaging drug trials.

Moving now to establishing clinical value or usefulness for disease detection indications, FDA

guidance notes that the clinical value of detecting a disease is often already well established by historical experience. If it is not, clinical value must be demonstrated within efficacy trials. For optical imaging drugs, determining the added clinical value over standard of care surgical treatment is also important.

Demonstration of added value is reflected in the trial designs for optical imaging drugs with disease detection indications. Intrapatient control design is often employed to allow sequential performance of standard of care surgery followed by investigational optical image-guided surgery. Advantage of this design includes efficient control of patient, tumor, and surgeon variability. Randomization of patients to a non-investigational imaging arm with typically less than a 1 to 1 allocation ratio is often employed to reduce bias that might otherwise lead to suboptimal standard of care surgery and overestimation of imaging drug performance.

A parallel arm control design can be used

when sequential intrapatient design is not feasible. It may also be needed if the value of detecting a disease or pathology is not established and clinical outcome data must be collected and analyzed. A parallel arm design also allows for controlled safety analysis. Of note, most imaging drugs feature relatively benign safety profiles compared to therapeutic drugs, given that they are administered only once or very infrequently and are typically pharmacologically inert.

I'll now describe an example of an optical imaging drug that has been approved for a disease detection indication to illustrate the trial design and endpoint considerations we have just discussed; hexaminolevulinate hydrochloride, trade name Cysview, is a heme precursor that accumulates preferentially in neoplastic cells and forms photoactive porphyrins. It was FDA approved in 2010 as an optical imaging agent indicated for use in the cystoscopic detection of carcinoma of the bladder. It is instilled into the empty bladder by a catheter, retained for 1 hour, and evacuated

prior to cystoscopic examination. Following standard of care white light cystoscopy, blue light cystoscopy is performed to identify red fluorescence in remaining additional neoplastic lesions.

Efficacy trials that supported Cysview approval enrolled patients who were clinically indicated for cystoscopy for known or suspected bladder cancer. The trials utilized an intrapatient control design in which patients first underwent standard of care white light cystoscopy, followed by subsequent blue light cystoscopy to identify additional fluorescent lesions.

Histopathology was collected as the reference standard for all lesions identified by either white or blue light, but negative findings were not systematically captured to allow calculation of sensitivity and specificity. Primary analysis determined the proportion of patients with additional bladder cancer lesions detected by fluorescence after standard of care cystoscopy and additional analyses evaluated the

frequency of false positive results. This trial design and these endpoints supported a disease detection indication for Cysview.

In today's presentations, we will see that the trials the applicant has conducted to support approval of Lumisight for its proposed disease detection indication utilized designs and endpoints that are consistent with guidance and precedent for optical imaging drugs. Lumisight trials use an intrapatient control design to allow primary analysis of added cancer detection by the drug over standard of care surgery. Of note, the applicant uses terminology of "cancer removal" for this co-primary endpoint which we consider to be essentially interchangeable with cancer detection and consistent with a disease detection indication.

As discussed, enhanced detection of cancer has been considered a clinically meaningful endpoint for approval of optical imaging drugs seeking disease detection indications, and patient outcome endpoints are typically not required. The preferred reference standard of histopathology was

collected in the Lumisight trials, and done so in a systematic fashion that allowed evaluation of not just disease detection rate and false positive results, but also more detailed assessment of sensitivity and specificity.

Given that the design and endpoints of the trials conducted to support the proposed indications of Lumisight are consistent with guidance and precedent, we can focus on whether the efficacy and safety results establish a favorable benefit-risk profile.

This leads me to today's questions and discussion points for the committee. The first point for discussion is whether the observed performance of Lumisight for patient-level detection of residual cancer, tissue-level sensitivity, and tissue-level specificity provides sufficient evidence of effectiveness.

The next point for discussion is the risk of serious hypersensitivity reactions associated with Lumisight and the adequacy of risk mitigation and assessment strategies under consideration; and I

want to reemphasize that these strategies are under consideration and they have not been negotiated with the applicant at this time.

Finally, a voting question for the committee is, do the benefits of Lumisight outweigh its risks? If yes, describe the clinically meaningful benefit and the risk mitigation measures that are recommended. If no, provide recommendations for additional data and/or analyses that may support a positive benefit-risk assessment of Lumisight.

This concludes the FDA introductory remarks. Thank you, and we look forward to the presentations and discussion.

DR. ROYAL: Thank you, Dr. Hofling.

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

For this reason, FDA encourages all

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

Likewise, the FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationship. 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 Lumicell's presentation.

Applicant Presentation - Jorge Ferrer

DR. FERRER: Good morning, everyone. I'm Jorge Ferrer, Chief Scientific Officer at Lumicell. Before getting started, I would like to thank the chair, members of the committee, the FDA, our investigators, and the hundreds of women who

participated in our breast cancer program for Lumisight and the Lumicell direct visualization system. Throughout our presentation, we will refer to this combination product as the LUM system.

The LUM system is a real-time, intracavity, fluorescence-guided imaging tool that improves the current standard of care by illuminating breast cancer during lumpectomy procedure. Let me walk you through the components.

Lumisight is an optical imaging agent that produces a fluorescence signal at the site of residual cancer. After completing their standard of care lumpectomy, the surgeon inserts the Lumisight DVS hand-held probe into the breast cavity to scan its surface and identify fluorescent signals from activated Lumisight, and thereby detect residual cancer. Lastly, real-time images are analyzed by cancer detection software and displayed to the surgeon on a computer screen to assist them in identifying the location of additional tissue to be removed.

The LUM system was developed to fill an

important need in patients undergoing lumpectomy. Lumpectomy is meant to be the minimally invasive alternative to mastectomy; however, surgeons lack the tools to see the extent beyond the initial specimen, limiting the effectiveness of the standard of care procedure. And this has consequences. In 19 percent of negative margins, cancer is still left behind, and 9 to 36 percent of patients have a second surgery due to a positive margin. All of this highlights the need for a real-time intracavity tool to enable surgeons to more effectively determine the extent of tumor for a more complete resection.

Let me show you a video of how this system works. Lumisight is administered intravenously via a 3-minute push 2 to 6 hours prior to imaging. Upon initial injection into the bloodstream, Lumisight is optically inactive. After injection, Lumisight is designed to be activated by enzymatic activity in and adjacent to the tumor, which cleave the molecules and allows tumor and a margin of healthy tissue to fluoresce, aligned with the

surgical goals of achieving negative margins. The imaging agent is designed to leverage the host immune response common in solid tumors.

After removal of the main tumor specimen and completing the standard of care procedure, the surgeon inserts the hand-held probe into the breast cavity, and in combination with the cancer detection software searches for residual cancer that might be left behind. When software identifies regions that are suspicious for residual cancer, those areas are displayed in red on the screen in real time. The surgeon will now take a targeted shape to resect the suspicious tissue, and once the tissue has been removed, the surgeon can rescan the cavity with the probe to ensure a more complete resection has been performed.

The LUM system is intended to provide immediate intraoperative feedback for the surgeon and typically takes less than 7 minutes to perform in the operating room. Our clinical development program consists of six studies in breast cancer in more than 700 patients. For today's presentation,

the efficacy will focus on the results from our pivotal study and the safety data will focus on all patients across multiple cancer indications injected at the proposed dose of 1 milligram per kilogram. The results from the pivotal study were published in the New England Journal of Medicine by the principal investigators, many of whom you will hear from today.

The proposed indication for Lumisight is for fluorescence imaging in adults with breast cancer as an adjunct for the intraoperative detection of cancerous tissue within the resection cavity following removal of the primary specimen during lumpectomy surgery. It is proposed to be used as a single dose of 1 milligram per kilogram, administered 2 to 6 hours prior to imaging.

The FDA has convened this meeting to hear your views on the benefit-risk of Lumisight and potential risk mitigation strategies. On the benefit side, the LUM system enables real-time intracavity detection and guided removal of residual cancer, most of which may have otherwise

remained undetected with current standard of care tools, as well as converting some positive margins to negative margins, which has the substantial benefit of reducing the need for second surgeries, and this is accomplished by removing additional LUM-guided shaves, which does not appear to worsen breast cosmesis. Overall, when used as an adjunct to standard of care, the LUM system improves surgical outcomes for patients. With regards to risk, only minimal amounts of tissue were removed guided by the LUM system. Furthermore, Lumisight was generally well tolerated with a low rate of serious hypersensitivity events.

Overall, you will hear from breast surgeons and other healthcare professionals that the benefits of removing residual cancer outweigh the safety risks that can be managed in the preoperative setting and through appropriate labeling. That being said, I want to state unequivocally that we take the safety events very seriously and have mitigation strategies to further reduce the risk of hypersensitivity events.

Our proposed mitigation strategies include clear labeling that informs users of the risk of hypersensitivity anaphylaxis, incorporating a new section into the pre-established device training program to address Lumisight warnings and precautions; an enhanced pharmacovigilance program to closely track and report hypersensitivity in anaphylaxis events; and a postmarket study to assess the incidence rate of anaphylaxis and hypersensitivity reactions in a broader population. I will describe each of these mitigation strategies in more detail later in the presentation.

Here is today's agenda and our list of presenters, all surgical oncologist presenters. Dr. Kelly Hunt, Shelley Hwang, Peter Blumencranz, and Barbara Smith were investigators in the pivotal study and have first-hand experience using the LUM system. These presenters are not being compensated for their time in preparation for today's meeting.

You will also hear from Dr. Tanya Laidlaw provide her opinion as an expert allergist, contextualizing the risk of anaphylaxis in a

healthcare setting. We also have additional experts with us today to help address your questions. These additional experts, along with Dr. Laidlaw, are being compensated for their time and travel for today's meeting.

Thank you, and I will now turn the lectern to Dr. Hunt.

Applicant Presentation - Kelly Hunt

DR. HUNT: Thank you. I'm Kelly Hunt, Professor and Chair of the Department of Breast Surgical Oncology at the MD Anderson Cancer Center. I also serve as the President of the Society of Surgical Oncology. I'm here today to discuss the challenges that breast cancer surgeons face during lumpectomy and what's needed to assist us and our patients in the surgical suite.

Breast cancer is the most common cancer in women. One in eight women in the United States will develop breast cancer in their lifetime. Let me share just a few more sobering facts about this life-threatening disease. More than 300,000 women were estimated to have been diagnosed with breast

cancer in the U.S. in 2023, with about 43,000 patients dying from breast cancer each year in the U.S. This makes it the second leading cause of cancer death in women in this country. As a result, every year in the U.S., 180,000 patients undergo a lumpectomy for a breast cancer diagnosis.

Caring for patients with breast cancer is very complex. Care usually begins with a mammogram, followed by a biopsy, and then a diagnosis. After diagnosis, lumpectomy is the most common surgical procedure to treat breast cancer. The goal of lumpectomy is to remove as much of the tumor as possible and a margin of healthy tissue to achieve negative margins.

Current intraoperative tools approved by the FDA all rely on ex vivo specimen analysis and attempt to predict the margin status by visualizing the tumor within the excised specimen or visualize the margin itself, but none directly assesses the presence of residual cancer within the surgical cavity. And so, although lumpectomy is the more common standard of care as compared to a

mastectomy, it can fail to achieve a complete resection.

An incomplete resection has been shown to more than double the risk of recurrence, and with recurrence, 1 in 4 patients will lose their lives; and when pathology finds positive margins a week after the initial surgery, the patient undergoes a second surgery. After surgical treatment, most patients will require adjuvant therapy and radiation, all of which carry the burden of potential morbidities.

Importantly, an incomplete resection and need for second surgery can have substantially negative consequences for our patients. These include the potential for increased patient anxiety, increased morbidity, and adversely affected cosmesis. Concerns about incomplete resections and second surgeries may result in patients opting for a mastectomy. Additionally, in patients with invasive breast cancer, second surgeries can delay initiation of systemic therapy and radiation therapy. Furthermore, a second

surgery, like any surgery, carries the risk of complications.

Currently, the presence of cancer cells at or near the lumpectomy specimen margins is used to infer residual cancer in the breast cavity, but this has limitations and challenges. The limitations inherent with standard of care lumpectomy intraoperative margin assessment techniques are well known. Excised breast specimens deform immediately after excision, causing surgeons and pathologists to lose specimen surface orientation relative to the lumpectomy cavity where the tumor may remain, even when the specimen is inked.

Handling and sectioning of specimens can expose tumor not actually at the margin, but nevertheless attributed to the margin. In addition, margin assessment is designed to find cancer that is connected to the original lumpectomy specimen but is ill-suited to identify non-contiguous lesions, and given the inherent limitations of examination, it's estimated that

less than 1 percent of the surface area is microscopically examined.

All of the above lead to declaring negative margins in 19 percent of instances when tumor remains in the patient; declaring positive margins where 65 percent of the time there is no tumor left behind; and a range of 9 to 36 percent positive margins, most of these requiring second surgeries.

To close, breast cancer is an all too common and life-threatening disease. The current tools we have for intraoperative margin assessment during a lumpectomy are limited to ex vivo analysis and do not identify the extent of tumor accurately enough, making it challenging to achieve a complete tumor resection. Ultimately, inadequate assessment of the surgical cavity during a lumpectomy procedure is further exacerbated by the inherent limitations of current margin assessment, which limit the physician's ability to accurately predict the presence of residual disease in the patient. This often leads to the need for second surgeries.

There is a clear need for an imaging system

that can examine the entire lumpectomy cavity in real time to facilitate the resection of cancer missed during the initial surgery to overcome the limitations of ex vivo tissue assessments and to improve patient outcomes and quality of life. Today we will demonstrate that the LUM system meets this important clinical need as an adjunct to standard of care that enables in vivo cavity assessment in real time for a more effective resection.

Thank you for your time, and I'll now turn the presentation over to Dr. Shelley Hwang.

Applicant Presentation - Shelley Hwang

DR. HWANG: Thank you, Dr. Hunt.

Good morning. My name is Shelley Hwang. I currently serve as Director of Breast Oncology Program at Duke University, and I'm one of the principal investigators of this study. This morning, I will share data from the pivotal study demonstrating Lumisight's ability to assess breast cancer lumpectomy cavity margins in real time and to facilitate removal of tumor left behind after

standard lumpectomy surgery.

With a goal of enrolling a representative group of patients, the study was conducted across 14 U.S. medical centers. These included ten academic centers and four community hospitals to ensure inclusion of a variety of investigators with different patient populations and surgical approaches.

Pivotal Study CL0007 was a multicenter, blinded, prospectively randomized trial in women undergoing lumpectomy for breast cancer. Patients were injected with Lumisight 2 to 6 hours prior to imaging in the preoperative area under medical supervision. The surgeon then proceeded to complete their standard of care procedure.

After the surgeon declared that they had completed their standard of care procedure, patients were randomized 10 to 1 to either LUM system-guided surgery or standard of care surgery without LUM system guidance. The randomization was designed to ensure that surgeons continue to perform their standard of care procedure without

any change in their usual practice in order to provide an unbiased assessment of the LUM system, where results after the imaging procedure were compared to the standard of care outcomes. As this rationale was the only reason for randomization, the study was not powered to detect differences between treatment and control arms. As such, the efficacy results we will review here do not include data on patients randomized to the control population.

Let me briefly describe the procedure for each lumpectomy followed by LUM system imaging. In the study, surgeons completed their standard lumpectomy surgery, excising the tumor with a rim of normal tissue. Commonly, surgeons also removed this additional tissue called shave margins according to their standard of care practice. All excised tissues were oriented in the operating room.

After the standard of care procedure was completed, the lumpectomy cavity was imaged using the LUM hand-held probe. For protocol, 6 images

covering the entire cavity surface were recorded. If the Lumicell signal was positive, as indicated by regions highlighted as read on the monitor, the surgeon removed a LUM-guided shave from that cavity orientation. Also per protocol, no more than 2 LUM-guided shaves were removed from any single orientation.

All tissue removed underwent routine histopathology assessment, consisting of sectioning and processing to determine the distance from the tumor to the margin. Positive margins were defined using standard pathology criteria. If a final positive margin was reported by pathology, the patient underwent a second surgery with standard pathology margin assessment. The LUM system was not used during the second surgeries.

Each LUM image was compared to the histology of adjacent tissue to classify the result as true or false. Positive LUM signals depicted in the top row were compared against the histology of the LUM-guided shave. The result was deemed to be true positive if the LUM-guided shave contained tumor

and false positive if it did not.

Negative LUM signals depicted in the bottom row were compared with the histology of the tissue excised from that orientation at a second surgery. The result was deemed to be false negative if the second surgery found tumor and true negative if it did not. If no additional tissue was excised, LUM negative signal was compared with the prior lumpectomy margin at that orientation. The result was called a false negative if the prior margin was positive and true negative if it was not.

The study was designed with three co-primary efficacy endpoints. The first endpoint was removal of residual cancer and was defined as the percent of patients who had residual cancer found in at least one LUM-guided shave. The other two co-primary endpoints addressed the diagnostic performance of the system. Sensitivity measured how well the system produced a positive signal in the presence of residual cancer in the lumpectomy cavity. Specificity measured how well the system produced a negative signal in the absence of

residual disease.

The study included multiple secondary endpoints to further assess efficacy of LUM guidance; however, for this presentation we will focus on the two most clinically relevant outcomes. These include the rate that patients converted from having positive margins to final negative margins and the impact of the LUM-guided shaves on the volume of tissue removed.

Lastly, we conducted an exploratory endpoint analysis to better understand the impact of the LUM-guided shaves on patient-reported cosmesis. For each of the three co-primary endpoints, performance goals were established prospectively and agreed upon with the FDA. The performance goal for the removal of residual cancer endpoint was based on published results for estimates of local recurrence, assuming that most local recurrences are due to residual cancer left behind during the initial surgery. Based on the reported 5 percent recurrence after lumpectomy with whole breast radiation, a performance goal of greater than

3 percent was established as an important clinical result that could impact the risk of incomplete cancer resection.

In Lumicell's prior feasibility study, standard of care margin pathology, which is completed several days after surgery with the excised specimen, achieved a sensitivity of 38 percent in predicting residual cancer in the lumpectomy cavity; therefore, based on this number, we targeted 40 percent for the performance goal. Also in the feasibility study, a specificity with a lower bound of 68 percent resulted in about one additional shave removed with a volume that other studies found to have had no negative impact on patient cosmesis or complication rates. To ensure a similar performance in the pivotal study, the performance goal selected for the specificity lower bound was 60 percent.

Inclusion criteria included female patients who are at least 18 years old and who had histologically or cytologically confirmed primary invasive breast cancer or ductal carcinoma in situ.

Patients were excluded if they were diagnosed with bilateral breast cancer or received neoadjuvant therapy. In addition, we excluded patients who were injected with blue dye for sentinel lymph node identification prior to LUM imaging. We also excluded patients with a history of an allergic reaction to polyethylene glycol or any oral IV contrast agent.

Key demographic characteristics of patients in the study were generally representative of the breast cancer patient population that would receive LUM guidance and consistent with the broader population undergoing lumpectomy in the United States. In this all female population, the average age was 62 years with the majority being of white race.

Accrual of black and Hispanic populations were relatively low at 6 percent and 3 percent respectively. This is consistent with publications which have shown lower clinical trial participation rates from minorities. The low accrual of black women, while not ideal, is not an outlier in breast

cancer clinical trials. Low minority accrual was further compounded by the fact that black women often present at later stages, and this trial enrolled patients with early-stage cancer, many of whom are diagnosed on screening mammography.

The average BMI was approximately 30, and 84 percent of patients were postmenopausal. Examining baseline tumor histology characteristics, the largest dimension of tumor in the main specimen was on average 1.7 centimeters. Approximately 70 percent of patients had invasive ductal carcinoma and 15 percent had node positive disease.

Now we'll turn to the efficacy results. The first primary endpoint in the pivotal clinical trial was the removal of residual cancer defined as the percent of patients in the study with cancer identified in at least one LUM-guided shave. LUM images detected and guided the removal of residual cancer left behind after the standard of care procedure in 27, or 7.6 percent, of all patients in the treatment arm. Thus, we achieved the removal of residual cancer metric with the lower bound of

the confidence interval above the prespecified performance goal of 3 percent.

Now we'll take a closer look at the extent of disease we found and its significance. Of the residual cancer removed, 13 of 27 patients had grade 3 tumors, the most aggressive form. Moreover, 20 of 27 had residual cancer measuring between 1 and 13 millimeters in size, which may have presented challenges to local regional control by radiotherapy. And finally, the residual cancer removed in LUM-guided shaves was missed by standard of care margin assessment.

Nineteen of 27 patients had all negative standard of care margins. The use of the LUM system resulted in removing additional cancer; that is, these patients would have completed their standard of care procedure with residual cancer remaining in the lumpectomy cavity and would likely not have received a second surgery, based on their negative standard of care margin pathology. Thus, the combination of Lumisight and Lumicell DVS facilitated the removal of high-grade, clinically

significant, and otherwise unrecognized cancerous tissue in 27 patients.

Now, for the sensitivity and specificity endpoints, we used the 2 by 2 matrix shown. Among 69 tissue samples determined to be positive on pathology, there were 34 correctly identified with LUM guidance with residual cancer removed, or true positives, for a sensitivity of 49.1 percent; however, the lower bound of the 95 percent confidence interval crossed 40 percent, and thus missed the performance goal by 3.6 percent. For the specificity endpoint, we achieved a specificity of 86.5 percent, with its lower bound exceeding the performance goal of 60 percent. Thus, we also achieved the specificity metric.

When considering the overall diagnostic performance, the system achieved an accuracy rate of 84 percent, exceeding the 50 percent expected from a random binary outcome, thus demonstrating its effectiveness for detecting residual cancer in the cavity.

Another performance metric of interest is

the receiver operating characteristics, or ROC curve, for the LUM cancer detection software. The ROC was built from the pivotal data and shows the trade-offs between sensitivity and specificity for the LUM system. The operating point in the pivotal study is shown along the ROC curve.

The area under the ROC curve provides a measure of the overall performance of the system. An AUC of 0.5 indicates a system that provides no discrimination, while an AUC of 1 indicates a perfect classification system. The AUC for the LUM system was 0.7, concorded with a 70 percent likelihood of correctly classifying residual cancer in the lumpectomy cavity. These results, combined with the previously mentioned accuracy of 84 percent, demonstrate the effectiveness of Lumisight to detect residual cancer in the lumpectomy cavity as an adjunct to standard of care.

As a secondary endpoint, we evaluated the ability of the LUM guidance system to convert positive margins to negative margins at the time of

initial surgery. Of the 62 patients with positive margins after the standard of care procedure, 9 patients, or 15 percent, were converted intraoperatively from standard of care positive margins to all final negative margins by removal of LUM-guided shaves. From these 9 patients, 8 avoided a second surgery by removal of these additional shaves. One patient still elected to have a second surgery; however, no cancer was found in the specimen in the second procedure.

Of the remaining 53 patients with positive margins, 45 proceeded to a second surgery with no cancer found in 28 or 62 percent. The anticipated direct benefits to the patient by avoiding a second surgery include faster time to next stage of treatment, reduced risk of infection, scarring, and the lower likelihood that some patients may elect to have mastectomy rather than re-excision for the second surgery.

We noted previously that in 8 of the 9 patients converted intraoperatively to final negative margins by removing LUM-guided shaves, no

cancer was found in the shave. Lumisight by design is activated in areas adjacent to the tumor, guiding the surgeon to excise a margin of healthy tissue, which is aligned to the surgical goal of achieving negative margins.

Thus, the positive signal in the instance of a LUM-guided shave with no tumor, or a false positive, is likely a result of the mechanism of action of Lumisight and is consistent with our prior studies, which showed a higher rate of a false positive LUM signal when tumor, either invasive cancer or DCIS, is closer -- so less than 2 millimeters -- or further away -- or more than 2 millimeters -- from the margin. Thus, it is reasonable to attribute the conversion to negative margins even when the LUM shave has no tumor to Lumisight's known mechanism of action.

With respect to our next predefined secondary endpoint, we evaluated the impact of the Lumicell system on total excision volume and cosmesis. When analyzing the 166 patients who had at least one LUM-guided shave removed, the mean

contribution of LUM-guided shaves to the total excised volume was 20 percent, with an average of 2 LUM-guided shaves removed per patient.

Finally, as an exploratory endpoint, patient-reported outcomes evaluating the impact of LUM-guided shaves to the patient's perceived cosmesis were collected in the pivotal study. We used a validated survey called the BREAST-Q, consisting of several pre- and post-surgery questions. As this was an exploratory endpoint, participation was optional. Overall, however, participation in this exploratory endpoint decreased at the longer data collection time points, which is expected in such surveys.

Results show that at every time point, the patient-reported Breast Cosmesis Satisfaction Score did not differ between those who did not, shown in blue, or did, shown in gray, have at least one Lumicell-guided shave. Thus, although the use of the Lumicell system resulted in removal of additional tissue with no cancer in some instances, these results suggest that additional tissue

resection driven by Lumisight did not worsen cosmetic outcomes.

Overall, our analysis shows that 35 patients, or 10 percent of the study population, had improvement in surgical outcomes by using LUM guidance as an adjunct to standard of care lumpectomy. Twenty-seven patients had residual cancer removed and 9 additional patients were converted intraoperatively to negative margins with the intraoperative excision of LUM-guided shaves, and one patient benefited from both.

In summary, of the three co-primary endpoints established together with the FDA, we exceeded the 3 percent goal for identification of residual cancer and found tumor in 8 percent of patients in the treatment arm. While the sensitivity endpoint missed the lower boundary of the 95 percent confidence interval, the LUM system exceeded the specificity endpoint of 60 percent with a point estimate of 86 percent and an accuracy of 84 percent for imaging residual cancer in the lumpectomy cavity.

The use of the LUM system enabled conversion of 15 percent positive margins to negative, sparing 8 patients second surgeries. The use of the LUM system removed only 9 percent additional tissue volume without worsening patient-reported cosmesis, and this was accomplished by examination of the lumpectomy cavity in real time by adding, on average, no more than 7 minutes to the overall surgery.

Thus, as concluded by the FDA, the pivotal study was an adequate and well-controlled study, demonstrating the effectiveness of the LUM system to detect residual cancer in the lumpectomy cavity following the standard of care procedure. These results also demonstrate clinical benefits that improve the current standard of care. This is the first and only imaging system that provides results in the lumpectomy cavity in real time, allowing the surgeon to use this information at the time of the initial lumpectomy procedure.

Thank you for your attention, and I will now turn the presentation to Dr. Blumencranz to review

Lumisight's safety data.

Applicant Presentation - Peter Blumencranz

DR. BLUMENCRANZ: Thank you, Dr. Hwang, and good morning. I'm Peter Blumencranz, Medical Director at BayCare Health System. I also served as a principal investigator in the pivotal study. I will provide a general overview of the safety results from the clinical program, and Dr. Laidlaw, independent expert allergist, will review the hypersensitivity and anaphylaxis events in detail.

Lumisight's safety profile at the 1-milligram per kilogram dose is well characterized with 726 patients exposed to this drug. Of these, 703 patients had breast cancer and 23 patients had other solid tumors. Importantly, the pivotal study provides us with more than 50 percent of the valuable safety population. For my presentation, I will focus on the overall safety evaluation from these 726 patients.

Per protocol, Lumisight was administered 2 to 6 hours prior to imaging at a dose of 1 milligram per kilogram by IV injection over

3 minutes. This was performed in the preoperative area under medical supervision, with all serious events managed immediately with standard interventions. Premedication in the clinical trial was not mandated but given at the discretion of the physician

The most common related adverse event was chromaturia, or discolored urine, which was expected due to the blue color of Lumisight and is also common with other approved treatments using blue dyes. These events are typically resolved within 24 to 48 hours. Nine hypersensitivity adverse events were considered related to Lumisight. Four of these were considered serious. In addition, 21 percent of patients experienced adverse events not related to Lumisight, including 4 percent experiencing seroma, 3 percent experiencing breast pain, and 2 percent nausea. Overall, few patients experienced a serious adverse event.

Related to administration of Lumisight, 3 patients experienced an anaphylactic reaction,

and one patient experienced a severe hypersensitivity reaction. Three patients had SAEs not related to Lumisight. Importantly, none of these events prevented patients from receiving standard of care surgery.

Now moving to adverse events leading to discontinuation from the study, in total, 8 patients experience related adverse events leading to study discontinuation. Three women experienced a hypersensitivity reaction and two experienced an anaphylactic reaction. Other events included extravasation, nausea, and skin discoloration. Lastly, all events resolved, and most resolved on the same day. Note that one of the SAEs of anaphylaxis did not lead to discontinuation, which is why only 2 anaphylactic events were presented here. Importantly, no deaths were reported during the study.

To close, Lumisight at a dose of 1 milligram per kilogram was well tolerated. All patients with adverse events and serious adverse events recovered and proceeded to receive their standard of care

lumpectomy procedure. I've personally used the LUM system in more than 65 patients. I felt comfortable using Lumisight and did not feel concerned about the safety profile, even with having two patients with hypersensitivity reactions. Thank you, and I'll now turn the presentation over to Dr. Laidlaw.

Applicant Presentation - Tanya Laidlaw

DR. LAIDLAW: Thank you, Dr. Blumencranz, and hello. I'm Tanya Laidlaw, Director of Translational Research in the Division of Allergy and Clinical Immunology at the Brigham and Women's Hospital and Associate Professor of Medicine at Harvard Medical School.

Lumicell engaged a team of three expert allergists to review the reported allergic reactions associated with Lumisight during the clinical trials. The three of us have reviewed each of the allergic reactions and hypersensitivity events reported. I would like to walk through each of the four serious hypersensitivity and anaphylaxis cases, including our collective

conclusions of each case. To note, these represent all related serious hypersensitivity cases across the entire safety population.

Let's first take a look at the cases overall. Our presentation will focus on a post hoc review of the four serious hypersensitivity and anaphylaxis events and potential etiology. To help ensure a complete assessment of determining if an event met the definition of anaphylaxis, we reviewed each event according to multiple anaphylaxis guidelines. Let's look at each case in detail.

The first patient who experienced anaphylaxis was first administered IV cefazolin before their Lumisight infusion. Within 1.5 to 2 minutes of starting Lumisight administration, the patient reported feeling chest tightness, dyspnea, upper body pain, and generally not feeling well, and was noted to have a red face. The Lumisight administration was stopped. The anesthesiologist was present and reported the patient as nauseous, diaphoretic, and dyspneic, appearing cyanotic and

apneic, with a weak pulse and a generalized rash.

The patient was treated with oxygen, epinephrine, steroids, and Benadryl, and transferred to the MICU for further treatment. Symptoms were all completely resolved within less than 12 hours. The patient was discharged the following day and lumpectomy was performed 17 days later. No allergy-related labs were sent for this patient.

By our independent review of this event, we classified this event as a life-threatening anaphylactic event probably related to Lumisight. Another potential etiology of this reaction could have been a cefazolin-induced reaction, as the timing was close. Additionally, the patient had a history of developing urticaria to iodinated contrast media; therefore, it was considered that this reaction may have identified a possible relationship between hypersensitivity to Lumisight and hypersensitivity to contract media. After this reaction, the study protocol was updated to exclude all patients with a history of reported allergy to

contrast agents or history of anaphylaxis to drugs containing PEG.

In the second event, the second patient was first given a nuclear medicine injection and image-guided insertion of wire 75 minutes prior to Lumisight administration, followed by oral doses of Tylenol and gabapentin administered 32 minutes before Lumisight. Within 2 minutes of starting the Lumisight administration, the patient reported experiencing nausea, vomiting, headache and lightheadedness, and was noted to have profuse erythema. The Lumisight administration was stopped.

At that time, the patient had been sitting upright and was reported to have a slightly lowered heart rate in the 50s and a blood pressure of 60 over 30. The patient was reclined and treated with IV saline, Zofran, and Benadryl, and her blood pressure recovered, and the symptoms resolved within less than 13 minutes. Her lumpectomy occurred the following day.

Allergy-related labs drawn a few minutes

after the reaction symptoms had resolved showed a blood histamine value above normal at 52, but it fell back to nearly normal within an hour, and the blood tryptase levels were slightly above normal at 11.5. We identified this as a severe, and because it involves 3 organ systems, anaphylactic reaction, probably related to Lumisight.

In the next event, 1.5 minutes into her Lumisight administration, the third patient reported experiencing dyspnea; a sense of tingling in the tongue, hands and feet; nausea; a feeling of a swollen lip; eye redness; and seeing black spots. Based on the report of these symptoms, the injection was stopped. Her heart rate at that time was normal at 88, with a normal blood pressure of 110 over 89. She was then treated with IV Benadryl, hydrocortisone, Zofran, and Pepcid. Her blood pressure increased to 163 over 114 over the next few minutes, and then normalized.

Most of her symptoms completely resolved within 20 to 30 minutes, and her lumpectomy proceeded to occur on the same day as this event.

Allergy-related labs showed blood histamine levels were slightly above normal at 55 right after the symptoms developed, and then it fell back to nearly normal levels of 11 within 30 minutes, though tryptase levels at 3.6 and 4.3 remained within normal ranges.

This was a moderate and possible allergic reaction probably related to Lumisight, but based on our assessment, not an anaphylactic reaction. The symptoms reported by the patient were largely subjective, including reported feelings of dyspnea and swollen lip; however, there were no objective signs recorded. Thus, we did not consider this case to meet the criteria for anaphylaxis based on multiple criteria, including those from NIAID.

Turning to our final narrative, during the 3-minute Lumisight administration, which was completed with the full dose, the final patient reported feeling funny with some itching in the hands, feet, and lips. Her vital signs had been normal throughout the infusion. She then developed hypotension over the next 15 minutes. She was

treated with fluids, lactated ringers, and placed in the reverse Trendelenburg position. Her blood pressure normalized and all symptoms resolved within 70 minutes. Approximately 3 hours later, after a needle localization procedure, the patient reported feeling lightheaded and experienced a vasovagal event. She was treated with ephedrine, and her symptoms resolved. Her lumpectomy occurred later that day. Allergy-related labs were drawn within 30 minutes of the reaction and again one hour later, with tryptase and histamine completely normal at both time points.

According to our assessment of this event, we consider this to be a moderate vasovagal reaction possibly related to Lumisight. This event was flagged, as it may meet criteria for anaphylaxis given the hypotension; however, isolated hypotension would be an uncommon presentation for anaphylaxis, and this is unlikely to be due to a hypersensitivity reaction due to the patient's symptoms resolving on IV fluids alone, without needing treatment with antihistamines,

corticosteroids, or epinephrine. No other organ system was clearly involved beyond cardiovascular with the hypotension.

Additionally, the completely normal blood histamine and tryptase levels make an allergic event even less likely. Thus, this reaction does not meet criteria for anaphylaxis based on multiple criteria, including NIAID. Due to this and the subsequent vasovagal reaction, we would classify this patient's experience as a vasovagal reaction and not an allergic reaction.

Revisiting the summary of these four events, our evaluation of the cases was similar to what was reported in the trial, but with some notable caveats. In one of the four, patient number 2, the classification was revised by the allergist from severe hypersensitivity to severe anaphylaxis because the reaction involved three organ systems, and anaphylaxis is just the term that we're trained to use to describe a hypersensitivity reaction that involved two or more organs. The severity remained unchanged.

In two of the four cases, the severity was downgraded, as both were not considered an anaphylactic reaction; therefore, according to our review, the anaphylaxis rate would have been 0.3 percent. In summary, all four patients had reactions that were quickly identified and managed, and went on to receive their standard of care lumpectomy procedure.

To put the risk of anaphylaxis in a clinical context outside controlled studies, the mortality rate from perioperative anaphylaxis is quite low, due in part because the allergic events are, by definition, happening in a monitored healthcare setting with trained staff and appropriate medical equipment available.

It is difficult to quantify the exact mortality risk due to anaphylaxis. The rate is expected to be particularly low in a preoperative setting because the patient is verbal and can communicate symptoms. Further, healthcare professionals are universally present in the preoperative setting post-injection. Importantly,

as it relates to Lumisight's administration during the trials, there were no deaths due to anaphylaxis or any other adverse event.

It's important to recognize that preoperative areas and operating rooms are already well equipped and well trained to manage anaphylaxis due to commonly used perioperative agents. For example, two relatively common causes of drug allergy perioperatively are antibiotics like cefazolin and blue dyes. Cefazolin is a frequently used cephalosporin and is the most common cause of perioperative anaphylaxis.

Cephalosporin antibiotic allergy overall has a prevalence of up to 2 percent, and cefazolin specifically causes allergic reactions in 0.5 percent of patients upon first exposure to it. Nonetheless, it's used very frequently, and in fact, 50 percent of the trial participants in the Lumicell study were given cefazolin in the perioperative setting.

Additionally, injected blue dyes for breast lymph node resections can induce allergic

reactions, with isosulfan blue having an approximate 2 percent allergic reaction rate. Even though these are relatively common reactions, the mechanism by which cefazolin or blue dyes causes these allergic reactions is not fully understood, and we don't have any clinical tests for them.

In summary, serious hypersensitivity events in the Lumisight clinical development program were infrequent, at a rate of 0.6 percent as reported in the trial or 4 out of 726 total patients. Whether the rate was 0.6 or 0.3 percent, these rates are low. Importantly, there were no life-threatening events after the eligibility criteria were updated. Furthermore, the label warns against an increased risk of potential adverse reaction in patients with a history of an allergic reaction to contrast agents or PEG. Also, although the etiology of these reactions is unknown, this doesn't affect identification or treatment for these reactions.

All events occurred at the healthcare setting under supervision of trained medical professionals equipped to manage such events, and

this preoperative setting was not specific to the clinical trial conditions or protocol. All clinical administration of Lumisight would be expected to only ever be done within a healthcare setting. Every patient fully recovered and proceeded to their planned lumpectomy procedure.

The risk of mortality is expected to be extremely low in the preoperative setting. Overall, in our clinical opinion, the observed rates of anaphylaxis and hypersensitivity are acceptable given the context of care and expectations for perioperative procedures and other medications used in these settings for breast cancer patients. All three of us as allergists would not have concerns about using Lumisight in the clinical setting.

Finally, I understand that you're asked to consider risk mitigation strategies to address hypersensitivity events. The sponsor's proposed mitigations, which will be covered next, are reasonable and sufficient to manage this rate of reactions. Thank you, and I will now turn the

presentation to Dr. Ferrer to expand on the safety mitigation strategies.

Applicant Presentation - Jorge Ferrer

DR. FERRER: Thank you, Dr. Laidlaw.

To reduce the risk of serious hypersensitivity events, the FDA is asking you to consider approaches to risk management. I will now present our view of what we believe to be appropriate risk mitigation strategies for the consideration of this MIDAC.

First, we are proposing a comprehensive label to further mitigate the already low risk of mortality due to anaphylaxis. The label includes clear mention of the risk of life-threatening anaphylaxis in the warning and precautions section. The label also advises healthcare providers to obtain the patient's history of allergy and hypersensitivity reactions before administration and indicates an increased risk in patients with a history of multiple food and drug allergies.

Very important, the label specifies to always administer Lumisight in a healthcare setting

and to have emergency resuscitation drugs, equipment, and trained personnel available. We also indicate to interrupt administration if hypersensitivity reaction is suspected and to monitor the patients for 15 minutes after injection.

As part of our device development, we have established a comprehensive training program for all users of the device, which was submitted to FDA as part of our PMA. The training will be conducted at each site before the system is used. This training includes video tutorials followed by hands-on practice. After Lumicell documents that the training has been successfully completed, the surgeon will receive their credentials to log into and use the Lumicell DVS.

We will now enhance this device training program by incorporating a training session, highlighting the characteristics of the drug Lumisight, including the risk of hypersensitivity and anaphylaxis, and emphasize the mitigation strategies established in Lumisight's prescribing

information. The surgeon will be instructed to inform staff of warnings and precautions and will also be trained in adverse event reporting for our enhanced pharmacovigilance program, which I will cover next. This training will also be available and offered to preoperative and OR staff.

For postmarket assessment, Lumicell has already partnered with a third-party vendor to support our medical information program with the goal of providing clear, accurate, and timely information to patients and providers, and our pharmacovigilance program to collect, evaluate, and report adverse events.

Because we take this risk seriously, we are proposing the following enhancements: implement Adverse Events of Special Interest program with increased frequency of reporting to the FDA to help identify safety signals sooner; train users on Lumicell's pharmacovigilance program to support a complete reporting process; and to standardize collection of additional data to help us learn more about the etiology of these reactions. We plan to

work with FDA to finalize the design and data collection of the enhanced PV program before implementation.

In addition to the enhanced pharmacovigilance program, Lumicell plans to initiate a postmarket study to collect additional information to further evaluate the incidence of anaphylaxis. A comprehensive data collection plan will be implemented, including baseline and post-injection vital signs, tryptase and histamine levels, and complete medical histories regarding allergies. The final study protocol, study size, and duration will be discussed in detail with FDA post-approval. We believe that the combination of our risk mitigation strategies are appropriate to raise awareness for the risk of serious hypersensitivity events and reduce their risk without the need of a boxed warning.

And now, Dr. Barbara Smith will close this presentation by providing her clinical perspective on the patient's impact of this technology to her patients.

Applicant Presentation - Barbara Smith

DR. SMITH: Thank you, and good morning. I'm Barbara Smith, Director of the Breast Program at Massachusetts General Hospital and Professor of Surgery at Harvard Medical School. I've been the lead PI on all the Lumicell breast trials. In fact, my team at MGH performed the first in-human use of Lumisight and the Lumicell DVS. All my work with Lumicell has been supported by NIH grants, and I have no financial interest in the company.

Today, I'm representing a number of stakeholders, my colleagues who you've heard from today and all the surgeon investigators and patients in our trial. We participated in this study because we recognize that the current system for margin assessment in breast cancer surgery is fundamentally flawed. Collectively, we believe that change is needed and that adding the LUM system to our current standard of care will provide real benefits for our patients.

As you've heard from my colleagues, current tools for lumpectomy margin assessment are limited

to ex vivo analysis of excised specimens. This approach does not identify the extent or location of residual tumor because it does not directly assess the cavity. Further, you've heard about the limitations of current breast cancer pathology assessment. Let me remind you of these limitations.

Pathology microscopically examines less than 1 percent of the excised and deformed specimen surface. This can't help but miss tumor, and we know it does because 30 to 40 percent of lumpectomy patients have an in-breast tumor recurrence if they have a lumpectomy alone without radiation. Even this limited analysis takes 1 to 2 weeks and requires a second surgery if margins are positive. Then, during the second surgery, we find that healing has deformed the cavity, further distorting the orientation of the tumor the pathologist sees in the excised specimen relative to where the residual tumor remains in the breast.

Sixty-five percent of the time in this study, and it's similar rates in other series,

re-excision for a margin declared positive by standard pathology shows no residual tumor. My patients and I must then ask ourselves, was this an unnecessary surgery due to a false positive pathology reading and there really wasn't any residual tumor, or was the pathology orientation reading incorrect, and the second surgery missed the residual tumor entirely? Quite frankly, in 2024, we should be doing better than this for our breast cancer patients.

Today you're being asked to evaluate and vote on the benefit-risk of an imaging system. While this system isn't perfect, neither is our standard lumpectomy pathology approach. In my opinion, this is an effective tool that addresses an important clinical problem. I believe that as an adjunct to standard of care, it can improve patient outcomes.

Here's what we know from the study. This system identifies the residual tumor where it remains in the lumpectomy cavity, guiding immediate targeted re-excision. The ability to immediately

re-scan the cavity then provides verification that the suspicious area has been removed. This eliminates the problems of specimen and cavity distortion that may currently misdirect the surgeon to the wrong cavity location during a second surgery.

Positive margins are also converted to final negative margins, which reduces second surgeries and the associated consequence of increased patient anxiety, risk of surgical complications, and worsen cosmetic outcome. The amount of additional tissue removed by the LUM system is modest and appears to have no impact on patient satisfaction with their breast appearance, and this is accomplished by assessing margins in the entire cavity during the initial surgery and adding less than 7 minutes to the surgical procedure. The data clearly show that as an adjunct to standard of care, the LUM system will help improve surgical outcomes for our patients.

With regard to risks, only minimal amounts of additional tissue were removed due to the LUM

system. Lumisight was generally well tolerated. The rate and magnitude of allergic reactions seen with Lumisight are the same or lower than those we see with the antibiotics, CT and MRI contrast agents, and node-mapping dyes we use every day in our breast cancer patients. Every perioperative setting where Lumisight would be used has the personnel and equipment to handle allergic reactions, which are a routine risk of what we do. We also believe that the risk mitigation strategies proposed are appropriate and will be sufficient to address the risks seen in our study.

Surgeons participated in these studies because we feel that standard of care margin assessment is inadequate; and importantly, patients were eager to participate because they were hoping to avoid a second surgery and avoid leaving tumor behind. Taking all this into account, I believe that the LUM system has the strong potential to improve care and outcomes for breast cancer patients. We hope that it will be made available to us and to our patients as soon as possible.

My colleagues and I respectfully ask for your favorable vote on the benefit-risk question. Thank you, and I'll now return the lectern to Dr. Ferrer to address your questions.

DR. FERRER: Dr. Royal, that concludes Lumicell's presentation.

Clarifying Questions to the Applicant

DR. ROYAL: We will now take clarifying questions for Lumicell. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon again after you have asked your question. When acknowledged, please 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.

At the moment I don't see any hands raised, so I'll ask the first question. I greatly enjoyed your presentations, and thank you for keeping to the time allotted. The one thing that wasn't included in the presentation was any information about this patient-specific software that's used to determine what areas are highlighted as being potentially having residual cancer tissue, and specifically with an ROC curve you can trade off sensitivity and specificity. I'd like to hear a little bit more about how the software works.

One of the things I noticed was on the display, in the lower left-hand corner, there was something about thresholds. It was not clear to me what that was all about and whether or not the software has been really optimized to provide the best sensitivity and specificity. So I'd like to hear a little bit more about the software.

DR. FERRER: I'm going to pull up slide 37, the one that has the ROC curve. The way we developed the algorithm, the cancer detection software, was by collecting information in our

prior study, what we call the CL0006.

DR. ROYAL: Yes.

DR. FERRER: There was a training set where we collected images and pathology data, and we used that training set to set the threshold for -- what we call the threshold, which is a -- the way it's done is that the surgeon needs to collect 6 images from the breast cavity, 6 images from anywhere in the cavity. The software then looks at those 6 images, gets metrics from these images to establish a baseline fluorescence for that patient, and then a multiplier, or what we call a threshold, is applied to those images, and any fluorescent signal that is above that threshold is going to be displayed in red.

So the way we did this, again, was with the CL0006 training set, and then we apply it prospectively to a smaller cohort in CL0006. And the trade-off here is like you mentioned; it's sensitivity and specificity. Sensitivity is finding cancer. Specificity is do not remove a whole lot of additional tissue that has no cancer

because the system is used on top of your standard of care procedure. So at this point, the surgeon had completed a standard of care procedure. They have removed any shave that they wanted to remove per standard of care procedure, and without Lumicell, that surgery would have stopped at that point.

So what we are trying to address is finding these small nodules of cancer that are left behind because the other main specimen is out, and balance that to how much tissue you need to take because now there's a relatively low prevalence of this residual cancer. So we did these trade-offs between the sensitivity and specificity, and I'm going to show you the ROC from slide number 37 from the core, where I'm showing the the operating point based on the results from the study.

So that was the region that we were targeting for in our study. Yes, that was the region that we were targeting for, for the study.

DR. ROYAL: So you've picked this point for the CL0007 study. Do you think that there's

another point on the ROC curve that would be better and would allow you to meet with the predetermined FDA goals?

DR. FERRER: So like I said, we have to lock the algorithm before going into the pivotal study. We do focus on constant improvements through a variety of mechanisms. So we have a quality process, we're going to have collective postmarketing data, and we're going to have commercial insights that will uncover additional opportunities, and in the future maybe adjust the algorithm; however, that will require additional clinical trials.

DR. ROYAL: Okay. There are a number of people who have their hands raised.

Cynthia Pearson, show your video.

MS. PEARSON: Thank you. I have two questions for Dr. Hwang and one for Dr. Ferrer, if there's enough time, and my first question for Dr. Hwang is about the sentinel node biopsy.

On page 50 of the sponsor's briefing document, you describe that for some patients for

whom the surgeon believes that they need to use blue dye to be able to do the sentinel node biopsy, the dye is put in after the resection procedure is completed. So I'm curious to know in how many patients was that done and what additional time did it add to the entire procedure?

DR. FERRER: Before introducing Dr. Hwang, every patient as part of the study, if they were going to have the blue dye injection, it had to happen after the Lumicell procedure. Yes, so that was part of the protocol, and the reason for it is because these blue dyes, they also fluoresce in the same wavelength of Lumisight. So if you inject the dye right in the breast before the Lumicell procedure, then you'll get fluorescent signal all over the place. So we limited that to the injection after the -- sorry; yes, after --

MS. PEARSON: Yes, that's all in your briefing book. Thank you for recapping.

DR. HWANG: Yes. And to briefly answer the question, 40 patients had injection of blue dye after they underwent the Lumicell procedure, and in

none of those patients was there any compromised inability to detect the sentinel lymph node.

MS. PEARSON: And about how long does that take to do that after the procedure? I'm sorry. This is a follow-up question. That was part of my original question.

DR. HWANG: So as part of the protocol, patients who are injected with blue dye after the Lumicell procedure were required to have injection followed by a 2-minute breast massage.

MS. PEARSON: Thanks.

And my second question I think is also for you. It's about the number of shaves that were taken in standard of care versus Lumicell guided. I may have have missed it, but I didn't see the actual number of shaves broken out by the two categories in the treatment group.

DR. FERRER: So we collected the information on the shaves prior to and after Lumicell. In the treatment arm, there were 190 patients that had no Lumicell shaves, there were 63 patients that had one shave taken, and there were 103 patients in the

Lumicell arm that had more than one shave taken.

I'm not sure if we have handy the number of shaves from the standard of care procedure. We can provide that information --

MS. PEARSON: Okay.

DR. FERRER: -- as necessary, but I would like to introduce Dr. Barbara Smith to comment on the comprehensive shave procedure.

DR. SMITH: So we implemented this protocol in a variety of settings with different surgeons. Some surgeons routinely will do their standard lumpectomy and take comprehensive shaves of the cavities because they feel that helps them. Other surgeons just take the main specimen, and only would take additional tissue if on palpation of the cavity or looking at the imaging performed of the excised specimen felt they had close margins. So we did not specify what the surgeon had to do for their standard of care practice because that does vary across different surgeons, but we were specific about what happened afterwards.

MS. PEARSON: Thanks. Thank you for that

response. I have one more quick question for Dr. Ferrer. Were any of the PIs in this trial black or Latino?

DR. FERRER: Yes. The answer is yes.

MS. PEARSON: Thank you, and that's all for me.

DR. ROYAL: Okay.

Dr. Applegate?

DR. APPLEGATE: Thank you. First, I will start with thanking all of the presenters for excellent and clear presentations and materials. I had a question -- and I may have missed it in the materials, but I wanted to understand what the learning curve is for using Lumicell and if there are any data on early results versus later results for the trial, for the different users, or how much variability there was. Thank you.

DR. FERRER: So we provided a training program that was consistent across all the study sites, and I'm going to introduce you to Dr. Kelly Hunt to talk about the usability of the system and the training.

DR. HUNT: Thank you for that question. There's certainly a learning curve every time we introduce new technology in the operating room, and before we entered patients into the pivotal trial, all of the surgeons were trained and performed the procedures as part of the lead-up studies, the feasibility study and so forth.

Surgeons usually say it takes about three procedures before they're very comfortable with the system, including using the camera and the software.

DR. APPLEGATE: Okay. Thank you.

This is just a clarifying question. To be very clear, Lumicell can be reinjected on the same day without, in general, safety risk if there's, for example, extravasation or a delay in the operating room access. I just want to make that really clear.

DR. FERRER: So in our study, we only allowed injection of Lumisight as a single dose, so there's no second administration of Lumisight. When the injection was interrupted, there was no

restarting of the injection.

DR. APPLEGATE: But it sounded like there was a patient who went the next day and had her lumpectomy, but it sounds like she wasn't reinjected.

DR. FERRER: Correct. That patient came back the second day and was not injected with Lumisight, and it was not attempted to be imaged with the device. The patient underwent regular standard lumpectomy procedure.

DR. APPLEGATE: Okay. Thank you.

DR. ROYAL: Dr. Greenberger?

DR. GREENBERGER: Thank you for the presentation so far. I have a couple questions. These focus on safety. The first I believe is for Dr. Blumencranz and maybe Dr. Ferrer or Laidlaw, and this has to do with the two reactions that are severe but they were not considered hypersensitivity or anaphylactic; in particular, one patient with acute respiratory failure and another patient, acute myocardial infarction and hypotension.

Can you share with us when the timeline was for those major outcomes?

DR. FERRER: Yes. I will introduce Dr. Laidlaw.

Sorry. We'll look into providing that information after the break.

DR. GREENBERGER: Alright. Thank you.

The second question has to do with the 14 patients that were in fact retreated with diphenhydramine, and no one had an adverse reaction. I assume this was after case number 1 of the anaphylactic reaction in the patient who was allergic to radiographic contrast material, but can you share with the committee the indications that were recorded that led to the diphenhydramine for those patients? Thank you.

DR. FERRER: So again, premedication was not mandated. It was administered based on the clinical judgment, and I would like to introduce Dr. Laidlaw to address the question.

DR. LAIDLAW: Thank you. So there were 14 patients who were prophylactically given

diphenhydramine, given Benadryl, prior to the infusion of Lumisight, and that was all based on the protocol at the treating physician's discretion. So those actually weren't used to treat any allergic reactions or hypersensitivity reactions; those were all just used for prophylaxis, and there were no specific indications actually ever listed for those uses. There were no uses of Benadryl to treat any other potential hypersensitivity reactions except those that were already listed and described in the material.

DR. GREENBERGER: Thank you. My question, though, is what was recorded as justification for the pretreatment with diphenhydramine?

DR. LAIDLAW: I'm going to turn to the treating physicians.

DR. HUNT: Thank you for that question. Oftentimes, at least in my center and I know some other centers, if we're using the blue dye for sentinel lymph node mapping, we will inject that as a premedication to prevent the allergic reactions for the blue dye.

DR. GREENBERGER: Alright. Thank you.

DR. ROYAL: Dr. Leitch? Marilyn Leitch?

DR. LEITCH: Thank you for the presentations. I have several questions. These are probably for Dr. Hwang about the pivotal trial, and then one probably for Dr. Laidlaw. So the comment was made, of course, about the blue dye and how that could not be used before the Lumisight part was done. I was wondering if you had other information about things like indocyanine green or Magtrace, and how you might have to alter the procedure based on the use of those.

I also had some questions -- this is maybe a technical thing -- about the depth of detection in the cavity of tumor cells. I was a little confused about the 2 millimeters on either side that was mentioned, something about that; and then if you had any thoughts about the histologic tumor type and detection, for example DCIS and invasive lobular cancer, and how that might contribute to accuracy.

And then the contribution to the false

negatives, I think it was kind of disappointing that not as many people were detected intraoperatively to resect, and do you think that can be use of the device in terms of does the surgeon actually interrogate the whole cavity or do you think there can be issues of training that could mitigate some of that?

Then, why there was no discussion of control since there was a control? I mean, I understand there are some statistical issues about it, but why have a control if you're not going to say anything about it?

And then for Dr. Laidlaw, what do you think of, if a person has no reaction to the Lumicell, but then let's say 5 years later, they have another cancer and mono-partial mastectomy, would there be contraindication to a second injection if the person had no reaction to the first? Thank you. Those are my questions.

DR. FERRER: Thank you. I will be addressing some of your questions, and I'll invite also Dr. Shelley Hwang and Dr. Laidlaw to comment.

In terms of the blue dye, the indocyanine blue, ICG, that you mentioned is an alternative. We have not studied using indocyanine green in our clinical studies, but that is a fluorescent dye, so it's likely that it may interfere. The Magtrace is not a fluorescent dye, so as far as I know, it might not be any issue with using Magtrace in conjunction of Lumisight.

To address your question on the 2 millimeters on the side on that plot, can we please bring up the core slide with the rate of false positive before, for DCIS and invasive, please? No. Sorry. I'm looking for the core slide on Dr. Hwang's section. Thank you.

I think you are seeking clarification on this slide. What this slide is trying to show is the rate at which the Lumicell signal generates a positive signal as a function of distance of the tumor from that margin. So the mechanism of action of Lumisight, again, it's not only targeting the tumor, but it's also targeting the invasive front, and it accumulates and it gets activated in

invasive front. So we are expecting that there's going to be sort of like a halo effect around the tumor where you get higher signal as you start getting closer to the tumor and lower signal as you move away from the tumor.

So the plot that is showing here on the left side is less than 2 millimeters. That's tumor -- either DCIS or invasive -- less than 2 millimeters from the edge. And remember, we're looking in the cavity, and when that tumor is greater than 2 millimeters, the rate of having false positive signal decreases substantially, and we believe that this is supportive of our mechanism of action for having this additional halo that would help achieve negative margins by taking the shaves that may not have cancer.

The other question was about false negatives. Can we please pull up the core slide on the four quadrants? Can we pull up the one with the numbers, please?

I'm going to show you a similar slide that was presented in the core, but this one will

actually have the numbers for the true positive, false negative, and false positives and true negatives. I think the question was more about the false negatives. So in our scenario when we have a negative signal in the cavity, if the patient ended up having a second surgery, and the second surgery found tumor, that was a false negative, and that happened 24 times. And the second scenario for false negatives is when there is no shave and the patient has a positive margin but there's no second surgery, so there's no additional tissue removed later to compare with the signal, and we consider those as false negatives.

One thing that is important to remember is that the system is used on top of the standard of care, so this additional cancer that we're detecting is cancer that would have been missed during the initial surgery, and I would like to invite Dr. Shelley Hwang to comment on the importance of finding this cancer.

DR. HWANG: So I'd like to add to what Dr. Ferrer was presenting here and would like to

reinforce the fact that even though 11 of the cases were counted as false negatives, because there was no additional tissue excised, we really don't have histologic confirmation of these false negatives; so they may have in fact been true negatives, so that's an unknown. We decided to count this as a false negative just with the abundance of caution, but I think when there are not histologic margins that coincide with that image, it's really difficult to determine what the gold standard is in those cases.

I'd like to respond to, Dr. Leitch, your question about the depth of tumor in the cavity. The technology allows us to detect tumor somewhere between 2 and 5 millimeters from the actual surface. Because there is a limitation to the depth of detection, we did not use this to do anything other than the lumpectomy specimen itself, but that is both a strength and a limitation of the technology in that tumor that's closer to the surface is more likely to be detected.

With respect to your question about DCIS,

invasive lobular cancer and other histologies that are less frequently identified, we were not powered to show the difference between different histologies, but we do have a slide that addresses the issue comparing invasive cancer either with or without DCIS and DCIS only. And on this slide, you can see that there really was no statistically significant difference, at least with the numbers that we have here, between invasive cancer histology and DCIS alone. We don't have a slide that demonstrates the response to your question about invasive lobular cancers.

Then finally, I believe I heard a question from you about how we designed the case with respect to the control population. I appreciate the opportunity to provide that clarification. This was reviewed in some of the FDA guidance documents, and the reason for the controls in this study was not to compare the technology itself between patients who did and did not get the Lumicell guidance; what we wanted to do is compare patients to themselves, so to compare the best

standard of care procedure that a surgeon could perform, and then to see within that patient how much better Lumicell could make those surgical outcomes.

Our intention was to use the control population to make sure that surgeons did not deviate from their usual practice by either taking a little bit less because they knew that the patients were going to be injected with Lumicell, or potentially deviating otherwise from their usual standard of practice because that would have really impacted our ability to compare within that patient what the result would have been with and without the Lumicell technology.

DR. FERRER: Thank you.

There was an additional question. There were two additional questions. I want to address one now, and I would like to invite Dr. Barbara Smith. There was a question about the training and if some of these false negatives were due to potential user issues, so I'm going to invite Dr. Barbara Smith to comment on how the system is

used and the training provided.

DR. SMITH: So as part of the training, the surgeon's instructed to use the device so that the window that's giving off the signal and picking up the fluorescence that comes back is methodically covered over the entire cavity. As one of the people who's done most of these cases, I think as I went along and did more, I realized about being meticulous, about being thorough, about adjusting how I hold the device to really not miss things, and I think that's something that would continue with use. But again, since this is on top of regular pathology and standard of care, every little bit of improvement a surgeon makes is still continuing to be an improvement over baseline.

DR. FERRER: And I'm going to invite Dr. Laidlaw to answer the final question about allergic reactions.

DR. LAIDLAW: So in terms of the use of Lumisight for a second administration years later -- five in this case -- five years later for a patient who did not develop any allergic reaction

or hypersensitivity reaction the first time, from an immunologic and an allergic standpoint, I don't think there would be contraindication to it, sort of speaking as an allergist. But clearly that was not done at all in the study and has not been studied yet, so that would be completely off label for the proposed label right now; therefore, we don't have any evidence one way or the other.

DR. ROYAL: Okay. I just want to comment that we have 10 panelists who have their hands raised, and we're planning to take a break at 11:45, so keep that in mind. If your question has been answered, you can lower your hand.

The next panelist is Dr. Bolch.

DR. BOLCH: Yes. Thank you, Dr. Royal, and thank you Dr. Ferrer for the presentation. I have just one question. In the standard of care, there is a high uncertainty as to residual tumor in the margin, and therefore the patients have subsequent conformal radiotherapy potentially with and without chemo.

For those patients in this study that had

the Lumicell device had additional surgeries to remove what was identified in the system, was there any impact to subsequent referral to conformal radiotherapy?

DR. FERRER: So in that study, we did not collect that information; however, what we ended up doing later was a post hoc analysis where we invited two independent radiation oncologists to look at our pathology data from 166 patients that had at least one Lumicell-guided shave, and the procedure was to look at these patients and make a determination of the radiotherapy treatment that the patient would have received after the standard, because we have that information, and the radiotherapy that the patient would have received after the end of the surgery -- I mean after the end of the Lumicell procedure.

So we look at that information, and I would like to invite Dr. Simona Shaitelman to talk about the results and her thoughts on the radiation therapy and the impact of Lumicell on radiation.

DR. BOLCH: Thank you.

DR. SHAITELMAN: Thank you very much for the opportunity. My name is Simona Shaitelman. I'm a Professor of Breast Radiation Oncology at the MD Anderson Cancer Center, and as Dr. Ferrer mentioned, myself, as well as Dr. Roberto Diaz, reviewed all of the cases to try to estimate would we have changed our recommendations as radiation oncologists based on what was done with the Lumicell system.

What we found was that 16 percent of patients would have had the option of actually more focal targeted radiation based on Lumicell leading to wider negative margins. So there are guidelines from the American Society of Radiation Oncology on who is eligible for partial breast radiation, and even within that, who can have even more focal targeted treatment. So by our sense, 16 percent of patients could have more focal targeting with the Lumicell device.

We also interestingly found that 3 percent of patients had negative margins after standard of care and would have technically been eligible for

omission of radiotherapy, but based on level 1 evidence; but then, because of Lumicell, an additional residual disease was found, ranging in size from 1 to 13 millimeters of disease, which is quite worrisome that potentially we'd be offering omission of radiotherapy to those patients who should not be getting it. Thank you.

DR. BOLCH: Very good. So in summary, the Lumicell system in residual margin surgery would not preclude radiotherapy, but it would definitely change the treatment planning.

DR. SHAITELMAN: So it depends on the radiation oncologist. I think for these patients with favorable breast cancers, there's a wide range of options, ranging from omission of radiation to a very accelerated radiation in just 5 days, to up to 4 weeks of radiation and focal targeted treatment. Our assessment was that the Lumicell system would potentially enable us to give potentially more patients omission of radiation because of wider margins or potentially more targeted treatments, but I think also highlighted for us the dangers of

not having as biologically a sound rationale of who should be omitted for radiation as we would have thought.

DR. BOLCH: Okay. Thank you very much.

DR. SHAITELMAN: Thank you.

DR. BOLCH: That's my question.

DR. ROYAL: The next person with a question is Dr. Burstein. Please remember to include your name and affiliation before asking your question.

DR. BURSTEIN: Hi. Hal Burstein from Dana-Farber. I want to congratulate my friends and colleagues for their very thorough work. I have several clinically oriented questions, largely for the surgical team. I think they build on a couple of themes we've begun to explore a little bit already, but just for my own clarification.

One is, any reason to be concerned that the procedure -- [inaudible - 2:37:30] --

DR. FERRER: It looks like we've lost audio.

DR. ROYAL: Yes. Well, we've lost audio and visual, so why don't we go on to Dr. Skates while Dr. Burstein reconnects.

DR. SKATES: Hi. Steven Skates, Massachusetts General Hospital. This is a great study, and I would just echo a few comments about the randomization. I wouldn't characterize it as a randomized study because that's not the main endpoint. The main endpoint is a within-person comparison.

The question I have is that in the FDA's presentations, they list the risks to benefits. The aim here is to ensure that the benefits outweigh the risks, and I'd like to quantify that on a per-patient basis rather than a per-excision basis, which seems to be the sensitivity and specificity analysis denominator here, because you've got only 357 patients in the study, but you've got an end of over 2,000 in your sensitivity and specificity calculation.

So my judgment of this procedure is that out of 357 patients that underwent this part of the study, 9 patients were helped in that they avoided a second-look surgery, so that's about 2 and a half percent. And any benefit is great, but there's no

indication in the presentation of the unnecessary surgeries, how many patients underwent surgeries where there was essentially no benefit, and the extra surgery, presumably, is a cost, at least to the patient, and presumably to the surgeon, and we can't get a sense of what that ratio is. In the slides on sensitivity and specificity, there is a 2 by 2 table, but that's, again, not at the patient level; but you do get a sense that there is 10 unnecessary or 10 false positive surgeries or excisions for every true positive.

So my question to the surgeons, such as Dr. Smith and and Dr. Hwang, is how many would be too many false positives per surgery? And what I'd suggest is setting a boundary there and showing that you're well above that boundary, and on a per-patient level rather than on a per-excision level here.

So could I get a judgment from the surgeons as to how many false positive surgeries per true positive surgery would be considered too many? What's the minimum level there? And then I would

like to suggest to the FDA to number the patients that were helped, the 9 patients who were helped, and get an estimate of the number of patients where there was this false positive surgery. Thank you.

DR. FERRER: I will address part of your question, and then I will invite Dr. Shelley Hwang to address the remaining of your question.

DR. SKATES: Thank you very much.

DR. FERRER: So to evaluate the diagnostic performance of the system, because the system is telling the surgeon on a point level which tissue to remove, we believe the right assessment for the diagnostic performance is the tissue level. We thought very hard and were very thoughtful about your comment about the patient-level assessment, which is also very important. What we believe is that the patient that benefited from this study, it's not just those 9 patients that were converted from positive margins to negative margins, but I'm going to show you a slide here when we are closing the efficacy section of the presentation.

There are those 9 patients that have removed

cancer -- sorry, conversion from positive margins to negative margins, but there's also those 27 patients that had additional tissue removed that was made during the initial surgery, and this initial tissue removed, it contained high-grade cancer, large in size, and also in 19 of those patients that will have negative margins.

But I'm going to invite Dr. Shelley Hwang to comment on your question about how much more tissue should be a boundary or not.

DR. HWANG: So I'd like to first address your question about false positives and provide some clarification on how we manage those patients during this trial. Patients who completed their standard of care lumpectomy and then had what appeared to be a positive image, the trial required that surgeons excise those margins that had the positive image. We did not get intraoperative determination of whether those margins were positive or not, and because we were very interested in this potential issue of a false positive, we limited the number of excisions we

would do on one margin or one orientation to two additional excisions beyond the standard of care, and we stopped there. So at no point did any of the patients who had a false positive require a second operation, so that's one clarification I wanted to provide.

But I think the issue that you're getting at is that those patients, nevertheless, had additional tissue removed, which did not contain tumor. We were very concerned about this issue, so that was the rationale behind determining how much additional volume was excised and whether that had any impact on patient-reported cosmesis, and those were the secondary and exploratory endpoints that I addressed towards the end of my presentation.

With respect to the question you asked about whether there could be a specific metric that could be used to determine the trade-off between true positives and false positives, we've discussed this among the surgeons, and I think for those of us who help these patients and care for them every day, I can't imagine a patient who would more rather avoid

one intraoperative excision than an additional surgery. So I think that number of false positives versus true positives would have to be quite high to make it so that patients would choose to avoid a second excision if the margin signal was positive there, because I think the downside of doing a second operation is so much greater than taking a little margin of additional tissue, as you saw in the video, intraoperatively.

DR. SKATES: Yes, that's very helpful.

Do you have a sense of the number -- there were 9 patients who avoided the second surgery. Do you know how many patients had a second -- not a second surgery but additional excisions that had negative margins? Is it the same order of magnitude? Was there nine or was there 90? Because that I think allows us to get a much better sense of how many patients were helped versus how many patients underwent additional surgery.

DR. HWANG: Yes. I'll just --

DR. SKATES: If you don't have at the moment.

DR. HWANG: -- quickly respond to that, and I think Dr. Ferrer has some additional comments.

So of the patients who had true positive margins, nine of those ended up having intraoperative excision of those margins due to Lumicell guidance and were able to avoid a second surgery, as we mentioned.

DR. SKATES: Right.

DR. HWANG: There were additional 45 patients who went on to the additional second surgery based on a histologically positive margin, and there was no cancer found in 28 or 62 percent of them.

DR. SKATES: Right. So the 28 is the one that may be comparable to the nine, where there's benefit to avoiding second surgery and there's essentially extra surgery that didn't benefit the patient. Is the 28 to the 9 the right comparison?

DR. FERRER: So just to clarify, there were 27 patients that had cancer removed after the standard of care procedure was completed, guided by the Lumicell device. There were 27.

DR. SKATES: Okay. Sorry. I'm worried about the ones where -- how many patients had Lumicell-guided excisions which showed no cancer?

You don't know that, right?

DR. FERRER: We --

DR. SKATES: Okay. Great. Well, we haven't been presented with data. Do you have a number?

DR. FERRER: We do. Give me a quick second. So what we're looking is for the number of patients that had a Lumicell-guided shave, and the Lumicell-guided shave had no cancer. Is that your question?

DR. SKATES: Yes, exactly.

DR. FERRER: Before I answer the question, I wanted to make a quick comment to Dr. Royal and the FDA. When we're trying to answer some of these questions, we want to share slides, but it looks like it's not allowing us to share slides. So when we try to bring them up, apparently they're not showing. We were asked if FDA can allow us to share slides?

DR. BURSTEIN: I don't wish to interrupt,

but I believe the question being asked can be answered on page 56 of your background materials, which is that there were --

DR. SKATES: And the answer is?

DR. BURSTEIN: -- 25 of 33 patients who had LUM-guided shaves had no residual cancer found.

Is that correct?

DR. FERRER: That is correct.

DR. SKATES: Okay. So then it's about 3 to 1, 3 patients with Lumicell-guided excisions for each patient with no cancer found to each patient who had cancer found and second surgery avoided. That's very helpful.

Then on the additional risk side, you've got 4 patients who had severe adverse events, all of which were managed. So I'd say that would be a fair summary of the risk versus the harms, and the sensitivity and the specificity really needs to be on a per-patient basis. Anyway, thank you very much for your presentation. I think this is a great study, and there's a very positive benefit here. Thank you.

DR. FERRER: Thank you.

DR. ROYAL: Okay. Dr. Burstein has rejoined the meeting, but I don't see his hand raised anymore.

Dr. Burstein, are you there, and did you want to ask your question?

DR. BURSTEIN: Yes. Thank you. Sorry. I guess the government didn't like the question I was going to ask or something. Thanks again, and congratulations to my colleagues who've been working on this, and a couple of quick questions for the surgeons. One is, any reason to think this would affect the utility or the diagnostic success of sensitive lymph node mapping procedures for patients? That was the first question.

The second question I had was regarding the standard of care operation. We know from the Chagpar study and others that a cavity-shaved margin is shown to reduce the likelihood of positive margins and actually reduce by half the likelihood of a re-operation. Given that, how would you contrast the surgical technique and

outcomes for a cavity-shaved margin versus the Lumicell-guided margin? Let me start with those two, and then I have two other ones, if I could.

DR. FERRER: I'm going to invite Dr. Barbara Smith to address those two questions.

DR. SMITH: Thank you. First, to talk about the sentinel node technique, all patients in the study, and I think for most patients having sentinel node biopsy, will have the Technetium 99 colloid injected first. The surgeon can check that they have a robust signal in the axilla, and many surgeons will just stop there and don't use blue dye. But if you want to use blue dye -- and I'm a fan of it myself -- it can be given after the lumpectomy is performed in the lumpectomy cavity.

In 40 patients, where I recorded this myself, we had 90-plus percent success of seeing blue dye in the node or in the lymphatics, in addition to what we were already getting from the radioactive dye. So it affects the sequence of doing the node but doesn't reduce the option of doing it at all, and it seems to work well with

this approach.

With respect to the margin approach, the comprehensive shave margins is a technique where you take more tissue in every patient, and it does improve the negative margin rate; however, it does also take more tissue in an unfocused way. In this study, even among surgeons who did comprehensive shaves as their standard of care and then took the Lumicell-guided shaves, additional tumor was found.

So the comprehensive shaves are still blind in terms of where you're targeting the excision. You get no feedback during the initial operation as to whether you've achieved a good margin or not, and we saw tumor still identified by this additional Lumicell intervention. So it is value added and has the potential over time to allow better outcomes, same-day information, and less overall tissue removed compared to comprehensive shaves.

DR. BURSTEIN: And I didn't see the materials. What approximate percentage of patients had comprehensive shaves as you described?

DR. SMITH: I think it was about 71 percent -- sorry; 71 patients had comprehensive shaves, and then another 165 had what surgeons deemed selective shaves. So they weren't taking them everywhere, but they were being guided by specimen images or palpation to take wider margins before they used Lumicell.

DR. BURSTEIN: Thank you. Another quick question is, of the 27 patients who had residual tumor, it looks like 21 of those cases, the residual tumor was DCIS, not actually invasive breast cancer, and I wonder if that should affect our thinking about the value of the procedure.

DR. SMITH: May I go ahead? Okay.

So we're pretty good as surgeons at taking out lumps of cancer. We can see them, the imaging studies can see them, so the most common thing we see in our margins is microscopic tumor that's either DCIS or other small deposits of tumor that imaging studies or palpation don't identify. So we were really happy that you could find DCIS with this system. That's one of our great challenges in

margin assessment, is this microscopic disease, so we were actually quite happy that that was detected significantly in our patients.

DR. BURSTEIN: Fair enough. And a final perspective question is, in contemporary practice with surgery, radiation, and adjuvant therapy, risks of local recurrence have become quite small. If you look at, say, the TAILORx experience, it's 2 to 4 percent at 9 years, so it seems improbable that you could do a lot better than that with standard therapy.

Do you think it would be valuable for an FDA label here to perhaps suggest that this might be appropriate in patients, as was suggested earlier by the radiation oncologists, who might avoid radiation therapy, and that that might be a more specific instance where the tool could be most helpful as opposed to all patients?

DR. FERRER: So at this moment, we do not believe to have a limitation for the patients, whether they're going to receive the radiation therapy or not, but I'm going to invite Dr. Simona

Shaitelman to address that question.

DR. SHAITELMAN: Hi. Thank you for that question. I think everything you're asking is hypothesis generating and I think where the field is moving to. In my view, I sort of view Lumicell as a step forward to having a more rational, thoughtful approach with patients when thinking about omission of radiation and also, again, de-escalation. We're really in the phase now of trying to give smaller and smaller targets of radiation to try and spare more normal breast tissue, as that's associated with better cosmetic result.

So I think hopefully if this moves forward, we can more thoughtfully have more nuanced conversations with patients about this. I agree, in general, outcomes are good, but for a patient who recurs, they 100 percent have recurred. So when we're offering omission, which we're doing more and more often, the more tools we have to guide that thoughtfully are important.

DR. BURSTEIN: Thank you all very much. I

have no further questions.

DR. HWANG: If I could, I just wanted to add one more point to Dr. Shaitelman's comment, which is that although the long term implications of the use of the Lumicell is an interesting one, especially in the context of omission of radiotherapy, the explicit endpoint of this trial, or one of them at least, was to determine whether we could help patients avoid re-excisions. And I just wanted to point out that the re-excision rate in the United States across all surgeons is probably around 20 percent, so our study and the results that we've shown today indicate that we really could make a substantial impact on that outcome.

DR. ROYAL: Okay. The next panelist with questions is Marie Griffin. Please state your name and affiliation.

DR. GRIFFIN: Yes. Marie Griffin, Vanderbilt. Hi. I have two questions, and one for Dr. Hwang. It seems like most of the patients who were positive by Lumicell actually had negative

margins, so 19 with negative margins were positive by Lumicell. Did any of them go on to have re-excisions or a second surgery because of the Lumicell results?

DR. FERRER: I will answer that question. Of the 19 patients that had negative margins and Lumicell removed a guided shave with cancer, there were two instances that that shave had also a positive margin. So these two patients ended up having a second surgery after the final pathology margin assessment declared that there were positive margins at the very end, and they went on to have a second surgery and tumor was found in the second surgery.

DR. GRIFFIN: Okay. So there were two additional surgeries and eight fewer, so six fewer altogether, I guess.

DR. FERRER: If you had those two, yes.

DR. GRIFFIN: Yes, but maybe more accurate.

Then Dr. Smith said something about anaphylaxis was similar in cefazolin compared to Lumicell. Is that anaphylaxis or just some kind of

allergic reaction? Because that's actually pretty high for anaphylaxis.

DR. FERRER: I'm going to invite Dr. Laidlaw to answer that question.

DR. LAIDLAW: So the rates that we quoted were the allergic reaction rates. We don't necessarily have great data to suggest of all of those allergic reactions, systemic allergic reactions, which ones would qualify as anaphylaxis with more than two organs since most of those were not discovered early on within a clinical trial with clear anaphylaxis guidelines but have been discovered afterwards. So these are really quite high rates of allergic reactions that we see quite commonly, and many of those are considered to be systemic allergic reactions as well.

DR. GRIFFIN: So would you say the rate of severe allergic reactions with cefazolin is similar to that with Lumicell?

DR. LAIDLAW: It's hard to compare apples to oranges without clearly controlled trials to compare that. I would say it's probably slightly

lower in cefazolin but, yes, relatively high compared to other [inaudible - 3:00:15], yes.

DR. GRIFFIN: Yes. I mean, because what I've heard is it's like 1 to 10,000, or something like that. I mean, it's not common to have anaphylaxis.

DR. LAIDLAW: Yes. I think overall it would be an uncommon thing.

DR. GRIFFIN: Okay. I'm just saying these aren't exactly comparable, really.

DR. LAIDLAW: No. The allergic reaction rates and the overall anaphylaxis rates are not the exact same number. True.

DR. GRIFFIN: Okay. Thank you.

DR. ROYAL: Next is Dr. Dykewicz.

DR. DYKEWICZ: Hi Mark Dykewicz, Saint Louis University, and two allergy-related questions. I think the first one most appropriately is directed to Dr. Ferrer. In terms of mitigation strategies with labeling, it's being proposed that there be a 15-minute observation period after completion of the administration of Lumicell. By some standards

that might be lower -- for instance, the duration -- and you would look at, in terms of observation after allergy, immunotherapy, or observation for anaphylaxis after certain biologics. So the question is how did you come upon the 15-minute interval?

DR. FERRER: Right. To come up with the 15-minute interval, we took these events very seriously. That's when we started engaging with our allergists, and even the anesthesiologists and our PIs, to get us enough information for us to start shaping up the risk mitigation strategies that we propose in the prescribing information. So it was based on a cumulative background and information provided by the reviewing team.

I would like to invite Dr. Laidlaw to comment on the specifics of the 15-minute observation time.

DR. LAIDLAW: Thank you. So that time frame was established because for all of the events that we saw within the trial and reviewed that were considered to be allergic or hypersensitivity

reactions related to Lumisight, all of those serious reactions occurred either during the infusion itself or very shortly thereafter; so none of them actually occurred more than 15 minutes after the infusion. And, in general, infusion-related reactions happen quite immediately and are uncommon to be delayed. On the flip side of that, more than 15 minutes of monitoring could interfere with patient care and didn't seem at this time to be warranted by the data we had. Thank you.

DR. DYKEWICZ: One of my questions would be, if we're looking at stating that there should be only 15 minutes observation, the concern would be whether there'd be less surveillance by staff after that point? We have a relatively limited number of patients in the big scheme of things looking for adverse events, and it is conceivable that with a larger number of patients, we would start seeing time frames of onset of anaphylaxis that may be later than that; so that's where my question comes with that.

But Dr. Laidlaw, actually one other question about the plasma histamine and the plasma tryptase levels. As you pointed out, elevated histamine and tryptase levels can suggest mast cell-mediated mechanism of an adverse reaction, but the timing of obtaining the specimens can be important because plasma histamine levels will peak at 30 minutes after onset of anaphylaxis, whereas tryptase levels will peak about 90 minutes after onset of reaction. So in terms of the patients that did have the histamine and the tryptase levels drawn, when were those specimens drawn? And what I'm implying is if the timing was not appropriate for tryptase, we could be getting some negative results for what was a mast cell-mediated event.

DR. LAIDLAW: Yes. For sure, the timing of the release and then the detection of histamine in the blood and then tryptase in the blood tends to follow sequentially, with a little bit more uncertainty about the timing of histamine. As guided by the FDA, those allergy-related blood draws done in patients 2, 3, and 4 were directed to

be done directly after the event occurred, and then 30 minutes later, which was true, and that was done for two of them.

One of them, it was some delay, so it ended up being 30 minutes later, then one hour later, and the peak in histamine in both of those was actually very quick, but it was in the blood draws done directly right after the infusion reaction, or potential infusion reaction, began, and then it came back down to normal within 30 minutes, suggesting there might have actually been a non-mast, cell-mediated reason for getting that histamine, either because of in vitro laboratory use and/or other things that happen in people that can increase histamine. And indeed, in general, the tryptase will peak more than an hour, sort of 1 to 2 hours afterwards, and we only have one patient sample that was drawn an hour after the reaction began, and that had absolutely no increase at all.

DR. DYKEWICZ: Okay. Thank you.

DR. FERRER: Before we move on, I would like to add something and invite Dr. Barbara Smith to

also comment. Like I said, in the prescribed information, we say monitoring 15 minutes. We're open for suggestions. However, when the patients are injected in the pre-op area, they remain in the preoperative area, and I would like Dr. Barbara Smith to inform the committee how these patients are monitored between the injection and the start of the surgery.

DR. SMITH: So thank you. Medications like this that are administered preoperatively are usually done with the patient on a stretcher, in a bay, vital signs monitored, with a nurse who's assigned to keep an eye on them. All of these patients will have an IV already in place because the IV is needed to give the Lumisight, so they're monitored between the time this is injected until the anesthesiologist actually then takes them into the operating room with an IV in place and in a bay with all the standard resuscitation equipment and personnel nearby. They're not going back to a waiting room or having this done at home or anything beforehand.

DR. ROYAL: Okay. Our next panelist with questions is Dr. Rosenthal.

DR. ROSENTHAL: Good morning, everybody, a fantastic presentation, and really enjoyed that. I have one simple question. Is the label going to say that the patient must be awake? I can't turn on my camera because it's turned off by the host. Jessica, I don't know if you can do that. But does it say specifically that the patient needs to be awake?

DR. FERRER: So the label right now doesn't specifically state that the patient must be awake; however, I would say the majority, all of them, all of these patients when they receive the injection, they're in the preoperative area and they are awake. They're not under anesthesia.

DR. ROSENTHAL: I understand that during the trial, but I wonder if -- one of the things you mentioned was that when patients were awake, they could comment when they were having a reaction, and if this label gets approved without that specifically on the label, I worry that a surgeon

could say, well, you know, "I want it now," and then they inject it after the patient has been put to sleep because they want it, and they may be working on a related procedure before they get to it.

So it just seems like I heard that when you first mentioned it, so I thought I would bring it up as something that might be an important risk mitigation.

DR. FERRER: So -- sorry, go ahead.

DR. ROSENTHAL: No, that's fine.

DR. FERRER: The label specifies that Lumisight must be injected between 2 to 6 hours prior to imaging. So we're hearing from our PIs here that no patient will go into anesthesia 2 hours prior to surgery. So in every case, the patient will be awake. Given that the label specifies that this has to be injected between 2 to 6 hours prior to surgery, it wouldn't be injected in any shorter amount of time.

DR. ROSENTHAL: It's just that off-label use is sometimes common among surgeons.

Okay. Then the other question was you said of the 9 patients, eight of those had actual negative pathology on the shaves that were Lumicell directed. Is that correct?

DR. FERRER: Correct. Those 8 patients, there were 8 patients that have a Lumicell-guided shave removed, converted from positive margins to negative margins, and the shave did not have cancer.

DR. ROSENTHAL: I see. And was that a sampling error, do you think? Or you stated it was diffusion related; it related to the diffusion of the imaging from the positive margin. I assumed the specimen had positive margins in that location, and that's why you're calling it a conversion.

DR. FERRER: Correct. In that same location, the patient had a positive margin in that same orientation, and we do believe that this is due to, I guess, what we've been calling the halo effect, where Lumisight is not just activated within the tumor but also in the surrounding tissue. And that was the results of the data that

we're showing on the patient; that when the margin is closer to the edge, you get a higher signal, a higher Lumicell signal, than when the tumor is further away from the margin.

DR. ROSENTHAL: That's different. I mean, that's just scatter probably. I mean, there could be scatter from the primary. I guess I just -- the location can be very hard to map back to the primary as well.

DR. FERRER: So, yes. I do agree that there are limitations of that, but not with the Lumicell system because the Lumicell system is looking right into the cavity, and the main specimen is the one that might be a little harder to do. But that's why we're doing this, because we want to check that cavity. And again, the surgeons are scanning the entire cavity, not just single orientations. They're scanning every single orientation, and they're recording images, every moving shaves when indicated.

DR. ROSENTHAL: Okay.

DR. FERRER: I would like to introduce

Dr. Dorothy Wong to comment on pathology.

DR. WONG: Hi. My name is Dr. Dorothy Wong, and I am the Chair of Pathology at Regional Medical Center and the Medical Director at what is now considered the UCSF affiliated hospitals in the San Francisco Bay area.

I did want to comment on the evaluation of shaved margins, and I wanted to say that even intraoperatively, when a surgeon sees tumor that looks like it's very close or at the margin, oftentimes these shaved margins end up being negative.

And was there a sampling error in these cases? I absolutely think it's possible. It depends on how these shaved margins were submitted. Were they entirely submitted, do we know where that potential positive residual tumor was? We don't, and if you are submitting a shaved margin that's large, it's very difficult to submit the entire specimen if you're submitting it to pathology, and either the pathology assistant, the resident, or the grossing pathologist misses that area or embeds

a section of that tumor on the wrong side, you may miss that as well. So that's just something to keep in mind on the pathology side. Thank you.

DR. ROSENTHAL: Thank you. And then my final question is, it seems like during these trials -- not during the pivotal trial -- there's been a change in breast care management, to some extent, with increasing the amount of patients that get pre-treatment chemotherapy. Was that in any way accounted for or did you have a wide range, or were these all previously untreated patients?

DR. FERRER: In our study, we excluded patients that have received neoadjuvant therapy because the goal of the neoadjuvant therapy is basically to destroy and remove the cancer, and when that happens, there might be tissue restructuring that may trigger more enzymatic activity in those regions. So because we didn't know exactly how the drug would be activated on these patients, we excluded that patient population from our studies. So we don't have data on that; however, we're conducting a study right now,

including patients that receive neoadjuvant therapy, but the results will be available much later this year.

I also want to introduce Dr. Kelly Hunt to comment on neoadjuvant therapies.

DR. HUNT: Thank you for that question. Certainly, the majority of patients with early-stage breast cancer will undergo upfront surgery, those with certain subtypes or more advanced disease that often would not be eligible for a lumpectomy and would go for neoadjuvant systemic therapy. So this technology that we're describing would still be eligible for the majority of patients who present with early-stage breast cancer who are candidates for a lumpectomy.

DR. ROSENTHAL: Thank you very much.

DR. ROYAL: Okay. We still have five panelists with questions.

Dr. Xiong?

DR. XIONG: Great. Chengjie Xiong from Washington University. I have a few maybe different questions. I will state all of them up

front, and you can add to or hear your comments.

Number one, we're talking about some of the specific lower bound that really is important to detect the efficacy of this new device. For example, you talk about 3 percent performance at patient level, and 40 percent sensitivity at tissue level, and 60 percent specificity at tissue level. So maybe you could let us know the background of how those things are chosen, especially given, if I heard correctly, some of the literature review you provide, like 9 to 36 percent of people will go out for a second surgery. So what is the, say, basis for that 3 percent of performance you're talking about? So that would be my first question.

The second question is, there is certainly variation in terms of the standard of care. Some could be very selective; some could be more comprehensive in terms of the sampling of the shaves. So you talk about 27 patients in total who are detected by this system with tumor, so how many of those are actually from less comprehensive standard of care during the initial stage of the

study?

The next one is more maybe a statistical question. The measurements are at the shave level, which is nested within the orientation, which it's then nested within patients. So there is a pretty complex data structure here. I just wonder how that structure is incorporated in those confidence intervals, which is the key statistic you provide to justify the efficacy.

I think those are all of my questions. Thank you for your comment.

DR. FERRER: So I'm going to address the first two parts of your question, and I may invite Dr. Doros to comment on the data structure. The the lower bounds were selected for each of the co-primary endpoints. I'm going to address the first one, the removal of residual cancer.

There are studies that have shown 5.3 percent of the recurrence followed by radiation therapy, and it is believed that part of these recurrences are due to residual cancer that remains in the patient after the initial procedure. So

going into the study, we know the prevalence of having residual cancer is relatively small, so we decided to use the 5.3 percent as our surrogate target, but because it's a prospective study, we decided to give some leeway here and establish a lower bound of 3 percent, meaning that in 3 percent of the patients, the lower bound of the detection of the removal residual cancer has to be greater than 3 percent, and that would be aligned with the 5.3 percent, more or less. So that was the reason for the 3 percent.

For sensitivity and specificity, we conducted our prior study and provided information for us to to start selecting these lower bounds for sensitivity and specificity. In the CL0006, we found a pathology -- sorry, the prediction of a margin on whether there was cancer in the cavity because we had that information. It was about 38 percent. So for the prospective pivotal trial, we thought, okay, this is pathology trying to predict cancer in the cavity, and this happens a week after, so we're going to be doing it in real

time. So we said we want to target somewhere around that area, so we picked 40 percent for our lower bound for the sensitivity input.

For the specificity endpoint, again, based on the prior study, it shows that with a lower bound of 68 percent or so, there was about 10 percent additional tissue removed at about 1 shave per patient, and we looked at literature from other studies that show that at that amount of tissue, patients don't appear to have a worsening cosmesis outcome, so we selected 60 percent. So that's why we selected all these endpoints.

The second question was about comprehensive shaves and selected shaves, and the performance among these these groups, so I'm going to show you a slide.

Do we know if we can share slides? Okay. So I'm going to share this slide with you. The slide is going to present the three co-primary endpoints and also the conversion from positive margins to negative margins per standard of care procedure. As we mentioned earlier, there were

comprehensive shaves, which means there are shaves removed from all around the cavity. There are selective shaves where the surgeon might go in and take a shave based on palpation, based on X-ray imaging, and based on different techniques that they have, or no standard of care shaves. And when we do these subpopulation analyses, we find that there's really no significant difference between the performance -- either sensitivity, specificity, and even the removal of residual cancer -- among these subpopulations.

To address your question about the data structure, I would like to invite Dr. Gheorghe Doros to address that.

DR. DOROS: Hello. This is Gheorghe Doros. I'm a Professor of Biostatistics at Boston University. I was involved in the conduct of the trial, being the independent statistician for the trial; and, yes, your observation is correct. We have kind of a nested data structure that needs to be accounted in the analysis part, and we did account that in the analysis of the data using the

generalized estimating equation with a compound symmetry working correlation structure.

Regarding the performance goal, for example, for the residual cancer, we know that the lower bound for the confidence interval, based on our data, is 5.6, which actually exceeds even the estimated value in the background data.

DR. XIONG: Thank you, and maybe just a quick follow-up in terms of the compound symmetry. Is that at the orientation level or the shave level?

DR. DOROS: This was shaves being nested within patient.

DR. XIONG: Okay. So orientation is not part of this.

DR. DOROS: Orientation was not part of the --

DR. FERRER: Yes, it is.

Sorry. Let me clarify. There is a tissue level and orientation level, so the tissue is removed from a specific orientation, so we kept track of the tissue and where the orientation from

the tissue was removed and the orientation of the image. So we have a matched pair of image per orientation and the tissue for that specific orientation.

DR. XIONG: Great. Thank you. I have no further questions.

DR. ROYAL: Alright. We have three more panelists who have questions. We're going to try to get through those questions. We're taking time from our break. We'll have the break after these questions. The next panelist is Andrea Richardson.

DR. RICHARDSON: Hello. I'm Andrea Richardson. I'm a pathologist at Johns Hopkins, and I keep getting moved to the back of the line, so as a result, a lot of my questions have already been answered.

I just wanted to know if anybody has looked specifically at possible explanations for the false positives and false negatives. For instance, in the false positives, was there a lower area of luminescence? In looking at your video, it seemed like there could be a broad area of luminescence

versus a pinpoint area, and we often see this in pathology with a positive margin that's very focal, and the re-excision will be negative. So has anyone looked at that?

In terms of the false negatives, I see that 11 of the cases supposedly had positive pathologic margins, but no additional tissue was taken. So I assume that those positive margins must have been very focal, otherwise they would have been taken back for additional surgery. Is that actually the case?

The other thing I was concerned about with the false negatives is, has anyone looked at the pathology? Since your luminescence is stimulated by the inflammatory response that surround most cancers, not all cancers have an inflammatory response, so lower grade DCIS, a lot of globular cancers don't have an inflammatory response. Were there more of these low-grade, non-inflammatory cancer types among your false negatives? And thank you for letting me ask questions.

DR. FERRER: To address the first part of

the question, I think you're referring to the size of the rate that is on the screen versus the rate of false positives. So we look at the data, and there is no correlation between the size of the rate shown on the screen versus whether the shave has cancer or not, so there was no correlation between the size.

So yes, there were several instances. There were actually eight instances where there was a positive margin and no second surgery was conducted. We do have the reasons for these specific 8 cases that this happened. Four out of these eight had closed the DCIS margins. One of these cases had not enough tissue to be taken because the margin was very close to the skin, and 3 of the 8 patients that didn't receive a second surgery went on to move to adjuvant therapies.

Then your final question was about false negatives. We looked at the subanalysis for different -- sorry; I'm trying to figure it out. I'm sorry. Can you repeat your third question?

DR. RICHARDSON: Was there an association

with lower grade, or lobular phenotype, or other non-inflammatory type tumors with your false negatives?

DR. FERRER: Thank you. Thank you for clarifying. So we did a subset analysis, a subpopulation analysis, for different tumor grades, and I'm going to be showing that, and it's going to show you the three co-primary endpoints and also the margin conversion rate for these different populations. We're looking at grades 1, 2, 3, and when you look at this set of populations, the confidence intervals are large. We don't really see a subset analysis. We don't see a significant difference between the endpoints for the study.

DR. RICHARDSON: Thank you.

DR. ROYAL: Okay. Dr. Dejos has a question. And please be concise with your question and concise with the answers. We're really running over time.

DR. DEJOS: Great. Well, thank you so much for that presentation. I have a two-part question here. How was causality determined in identifying

your adverse events? I recognize that nausea, breast pain, seroma were not related to Lumisight, so I'm curious if you guys used Durango [ph] or other types of causality tools.

DR. FERRER: So the way the causality or the relatedness was assessed was essentially the physician treating the patient, understanding the reactions and having a conversation also with an independent medical monitor and also our data safety monitoring board. And there were discussions about these reactions, and there was a consensus or input was provided to the physician to determine whether the adverse event was related to the injection or not. And there were different categories; there's probably, likely, so we establish for each one of these different categories for probability of relatedness.

DR. DEJOS: Great. And if I understand your slide here, on slide 46, you or your teammate mentioned that nausea was not related to Lumisight, but in two slides after that, we see that nausea led to the discontinuation of Lumisight. Could you

clarify that?

DR. FERRER: Yes. So when nausea was reported for these patients -- I think it's the same one -- it happened while administration of Lumisight was being conducted, so that led to the interruption of the dose.

Do we know if this nausea is the same one? And it was related?

I'm going to invite Dr. Kelly Hunt to address that second part of that question.

DR. HUNT: Thank you. So often, nausea is seen in our patients around the time of surgery, often related to anesthesia administration, so we did report when we saw nausea in the perioperative setting, but it was, in many cases, not felt to be related to Lumisight because it was well after the surgery, often in the recovery room and the recovery period.

DR. DEJOS: Okay. Thank you. Because two slides from the current slide that's being shown states that it was related to Lumisight, so that's why I was a little confused.

DR. HUNT: Yes. So I think it's because it was related when it was during the injection as part of the hypersensitivity reactions, but we did record when patients reported breast pain afterward, even though we expected breast pain from breast surgery, and we recorded when they had nausea, as we often, unfortunately, see in many of our patients related to anesthesia administration.

DR. DEJOS: Great. Thank you. And then for extravasation, I recognize that 2 out of the 4 patients were discontinued Lumisight as well. How was extravasation managed in that setting? I recognize it's preoperative. Are you guys using primarily cold packs, hot packs, any unique antidote?

DR. FERRER: I'm going to invite Dr. Barbara Smith to answer that question.

DR. SMITH: Yes. These were related to the IV infiltrating during the procedure. The patients, we used warm packs on them, but none of the patients had particular pain or other skin changes other than the color. But since this was a

new agent and we didn't have experience with this, we stopped the protocol for any time we saw this, and it turned out that blue color resolved over time in the two patients that had it and had no skin changes that persisted.

DR. DEJOS: Thank you. That answered my questions.

DR. ROYAL: Okay. If we could have the final questioner, Dr. Hackney.

DR. HACKNEY: Hi. Thank you. I hope this will be a quick answer. There are concerns about the recommendation of 15 minutes of monitoring after the injection, and I'm trying to understand what would happen to the patient after that 15 minutes because they're still going to have their IV in. They're still going to be in the pre-op area. I guess the only thing you could say is you could stop monitoring blood pressure, heart rate, O2 sat or something after 15 minutes, and I guess I wonder since you don't have enough data to know how long after injection the reactions could occur, why not just keep them on through monitoring

until after the surgery's over? Thank you.

DR. FERRER: I'm going to invite Dr. Barbara Smith to answer your question.

DR. SMITH: So in the protocol, and I think what we're talking about for this 15 minutes, is that it would actually be very frequent monitoring, perhaps with the nurse at the bedside talking with the patients, looking for any other symptoms or things. Certainly, these patients are in the monitored situation between this time and when they go to the OR, during the OR, and afterward, so we think that perhaps a bit more intense monitoring early on, which is when we saw the side effects that we thought were attributed to Lumisight, and then go back to standard of care thereafter, which is still pretty well monitored.

DR. HACKNEY: Thank you.

DR. ROYAL: Okay. We're 20 minutes behind schedule. [Inaudible - off mic].

DR. SEO: Dr. Royal, this is Jessica speaking. It looks like you're muted. If you are still speaking, if you could unmute, please.

DR. ROYAL: Sorry. We're 20 minutes behind schedule, so we're going to take a quick 10-minute break. Panel members, please remember there's no chatting or discussion of the meeting topics with other panel members during the break. We'll resume at 12:17. Thank you.

(Whereupon, at 12:05 p.m., a recess was taken, and meeting resumed at 12:17 p.m.)

DR. ROYAL: It is now 1217. We'll proceed with the FDA presentation, starting with Dr. Shane Masters.

FDA Presentation - Shane Masters

DR. MASTERS: Hello. My name is Shane Masters. I'm a clinical team leader in the Division of Imaging and Radiation Medicine. I appreciate this opportunity today to discuss an overview of the clinical data for Lumisight.

The active moiety of Lumisight, pegulicianine, is a molecule that contains a fluorophore and a quencher, separated with a peptide linker. When the fluorophore is held in proximity to the quencher, as in the intact

molecule, it is optically inactive. Cleavage of the peptide linker by cancer-associated proteases allows the fluorophore to separate from the quencher and become optically active.

As you heard this morning, Lumisight is the drug component of a combination product. The product also has a device component called the Lumicell Direct Visualization System. This device images the fluorescence from cleaved Lumisight. It includes a hand-held probe that is capable of imaging inside a lumpectomy cavity, as well as a tumor detection algorithm to identify areas that have enough fluorescence to be considered suspicious for residual cancer. The proposed indication for Lumisight is for fluorescence imaging in adults with breast cancer as an adjunct for the intraoperative detection of cancerous tissue within the resection cavity, following removal of the primary specimen during lumpectomy surgery.

So I'll start by discussing the design of trial CL0007 from the FDA perspective. CL0007 was

a prospective trial conducted at 14 sites in the United States. It used a two-arm randomized blinded design that was intended to reduce the potential for surgical bias. The randomization was at 10 to 1 between the active arm and the control arm, and this study was not powered for comparison between the arms. It did, however, use an intrapatient control design.

As Dr. Hofling discussed this morning, this type of design is often used in optical imaging drug studies, and it has efficiency advantages in controlling for patient and surgeon variability. Important enrollment criteria in the study were that patients were adult females who had either known primary invasive breast cancer with or without ductal carcinoma in situ or ductal carcinoma in situ alone. All patients were required to be scheduled for breast-conserving surgery, and they were not allowed to enroll if they planned to receive neoadjuvant therapy.

All patients in CL0007, as I mentioned earlier, were to receive Lumisight prior to

standard of care breast-conserving surgery. Once standard of care surgery was complete, patient randomization was revealed to the surgeon. Patients in the control arm had no further surgery, while patients in the active arm had additional surgery that was guided by Lumisight. Lumisight imaging in this study will be described shortly. All specimens that were removed from the patients in both arms were assessed by histopathology.

So as we mentioned, all patients in CL0007, whether in the active arm or the control arm, were to receive Lumisight using the same regimen. This was 1 milligram per kilogram of body weight administered intravenously over 3 minutes. Administration was to occur 2 to 6 hours prior to intraoperative imaging. This is the same dose and M timing [ph] that is proposed for the to-be-marketed product.

Surgery in the study started with a standard of care lumpectomy. A lumpectomy produces a lump or main specimen and creates a cavity in the breast where the lump used to be. In the study, the lump

and the cavity were both divided into 6 orientations that were based on anatomic axes as shown on this slide. The lump is intended to contain a complete tumor; however, this is not always possible, so after the lumpectomy, additional specimens could be taken from the cavity, also considered part of the standard of care surgery. These specimens termed shaves could be selective where a surgeon suspects there was some residual cancer or other abnormality in the cavity and excises it.

Alternately, they could be comprehensive, where the surgeon systematically removes the specimens from every orientation of the cavity, regardless of whether they suspect an abnormality. Some surgeons perform comprehensive shaves routinely to attempt to remove occult cancer from the cavity.

There was no limit to the number of shaves that could be taken as standard of care, and the goal of this surgery was to obtain a complete resection of cancer just as in clinical practice.

After the standard of care surgery was complete, the randomization was revealed, and if a patient was in the control arm, surgery was concluded. For patients in the active arm, surgeons were instructed to take additional shaves as directed by the tumor detection algorithm of the Lumicell Directed Visualization System.

A specimen that was removed because of Lumisight positive imaging was termed a therapeutic shave. Surgeons could take up to two therapeutic shaves per orientation. The type and orientation of all specimens was recorded, and local pathologists performed routine histopathologic analyses for all specimens, blinded the identity for shaves whether they were part of standard of care surgery or therapeutic.

Each specimen was evaluated by pathologists for the presence or absence of cancer. If a specimen contained cancer, it was also evaluated for margin status, and it's important to distinguish between these two results for the purposes of this study, and we'll talk about why

that is shortly. Margin status reflects the presence or absence of cancer within a certain distance of the surface of the specimen that used to be in contact with the cavity, and when positive, indicates an increased risk for tumor recurrence.

In patients who had invasive cancer, regardless of whether they also had DCIS, a positive margin was defined as tumor on ink, that is, tumor cells present at the relevant surface. In patients who had DCIS only, a positive margin was defined as cancer within 2 millimeters deep to the surface that used to contact the cavity. These definitions are taken from consensus guidelines released by the Society of Surgical Oncology and American Society of Radiation Oncology. At an orientation level, the margin status is determined by the outermost surface of the last excised specimen. A patient is considered to have a positive margin if any orientation has a positive margin.

Now, this margin status, as you've heard, is

not known during surgery in this study or in practice because the results of permanent section histopathology take multiple days to be obtained. However, we can assign retrospectively a margin status to orientations and to patients at various points in the surgery. Two important points that had margin status assigned in CL0007 were at the end of standard of care surgery; that is after lumpectomy and any standard of care shaves were complete, and that's termed a standard of care margin; and then the Lumisight margin status, which is after all therapeutic shaves were complete.

Imaging was performed with the Lumicell Direct Visualization System at multiple time points during CL0007. The first images were obtained at cavity initialization, after the lumpectomy portion of the surgery was complete but before any shaves were taken. The entire cavity was imaged with the tumor detection algorithm disabled, and the resulting images were used to determine the signal intensity threshold for the tumor detection algorithm.

The second round of imaging was optional, occurring only if shaves were taken as part of standard of care surgery. In that case, orientations where a standard of care shave were to be taken were imaged, again, with the tumor detection algorithm disabled, and those were used for exploratory analysis.

The third time images were obtained was after completion of standard of care surgery, and that was only in patients who were randomized to the active arm. This involved imaging the entire cavity with the tumor detection algorithm enabled and shown to the surgeon. It was intended to obtain the images for the main analyses of the study.

Some of the analyses in CL0007 were performed at what was termed a "tissue level." For these tissue-level analyses, a tissue could be material that was removed from the patient -- in other words, a specimen -- that was sent for a histopathology, but it could also be material that was left in the patient. In most cases, a tissue

is represented by one image from the Lumicell Direct Visualization System. Each orientation from each patient contributed 0 to 3 tissues to the analysis.

An orientation that could not be shaved -- for example, something that was very close to a skin surface of the chest wall -- was not to be imaged, and that accounts for the zero tissues end of the range; otherwise, the number of tissues in each orientation was generally equal to the number of therapeutic shaves plus one, because after each therapeutic shave, another image was obtained.

In some cases, it was necessary for the surgeon to combine two orientations into a single image or tissue -- for example, if the cavity was relatively small -- and the reason for going into this level of detail is just to explain that the number of tissues is not necessarily equal to the number of patients times the number of orientations.

The reference standard that was used for

tissue-level analyses was a hierarchical histopathology-based standard. The highest level of the reference standard, which was used whenever a therapeutic shave existed, was whether cancer was found in that shave. If a therapeutic shave did not exist, the second level of the hierarchy was based on whether cancer was found in a second surgery. If a therapeutic shave and a second surgery were not available, then the third and final level of the reference standard was assigned using the margin status from the previously excised specimen.

In Study CL0007, the large majority of tissues, about 81 percent, were assigned a reference based on prior margin status; however, among the reference standard positive tissues, the largest contributor to the reference standard was presence of cancer in a therapeutic shave, and the second largest was presence of cancer in a second surgery.

Patients randomized to the active arm could be included in up to three populations in this

study. The safety population included all patients who received any dose of Lumisight. The modified intent-to-treat population was a subset of the safety population that excluded patients who could not be imaged with the Lumicell DVS, and this was the primary patient analysis population. There was also a per-protocol population, a subset of the modified intent-to-treat population, that did not have any major protocol deviations, and that was used for the sensitivity analyses.

There were three co-primary endpoints in CL0007: patient-level removal of residual cancer, tissue-level sensitivity, and tissue-level specificity. The patient's level removal of residual and cancer endpoint was defined as the fraction of patients who had cancer found in at least one therapeutic shave among all patients. Sensitivity and specificity are very often used to assess performance in studies of imaging drugs with disease detection claims, and the 2 by 2 table and formulas shown on the slide there are typical.

The applicant defined multiple secondary

endpoints in the study. We selected a subset for discussion in today's FDA presentations. Conversion rate is the proportion of patients who had pathology positive margins after standard of care surgery for whom therapeutic shaves resulted in pathology negative margins. This was assessed both in patients with positive margins after standard of care surgery, as well as among all patients in the modified intent-to-treat population.

Because patients with positive margins after breast-conserving surgery often receive additional surgery, the patients who convert their margin status through Lumisight-guided shaves stand to benefit from avoiding a second surgery. We'll also discuss patient-level sensitivity and specificity, volumes of specimens removed in therapeutic shaves and their contribution to total specimen volume, and patient satisfaction survey results.

CL0007 screened 490 patients and enrolled 406 of them, all of whom received Lumisight. Fourteen patients withdrew from the study prior to

randomization, leaving 392 patients to be divided into the active arm, which in this case constituted the entire mITT population and the control arm at the 10 to 1 ratio. Ten patients were considered to have major protocol deviations and excluded from the per-protocol population.

As you heard this morning already, the age of patients that participated in Study CL0007 is similar to what we would expect for United States patients with breast cancer. The study enrolled predominantly white, non-Hispanic patients. Distribution of tumor histology and receptor status are also similar to what we would expect for the United States patients who had breast cancer. The most common tumor histology in the study was invasive ductal carcinoma with or without ductal carcinoma in situ, representing about 70 percent of the modified intent-to-treat population.

We did note that the proportion of patients with triple negative breast cancer is lower than recent estimates among all patients with incident breast cancer, but that's likely due to the study

enrolling patients who are clinically indicated for breast-conserving surgery without neoadjuvant therapy, as triple negative breast cancer is typically more aggressive.

Margin status at the end of standard of care surgery is an important baseline characteristic of this study because it's expected that Lumisight would have the greatest potential to benefit patients with positive margins after standard of care surgery, so the standard of care margins were positive in 17 percent of patients in Study CL0007. This did not appear to be driven by any single surgeon, as the range of margin positivity after standard of care surgery among the four surgeons who operated on 20 or more patients was 9 to 18 percent.

Next, I'd like to discuss the design of Study CL0006. CL0006 was a single-arm, multicenter trial that was intended to refine the algorithm used by the Lumicell Direct Visualization System for detection of cancer. At a high level, the design was similar to Study CL0007; however, there

were some important exceptions. CL0006 had no hypothesis-tested primary endpoints, though it was analyzed retrospectively using the same framework as CL0007. There was no control arm to address potential surgical bias.

Because the study was intended to refine the tumor detection algorithm, the algorithm was updated during the study after an interim analysis. The refined algorithm was based on results from the first 83 patients enrolled, and 44 additional patients were enrolled in study using the original algorithm. A validation set of 103 patients were studied using the refined algorithm, which was the same algorithm used in CL0007 and intended for marketing.

The demographics among enrolled patients in CL0006 was very similar to that of CL0007. The baseline tumor characteristics were also similar to Study CL0007, though more patients had some preoperative lymph node status assessed in this study. The margin status after standard of care surgery was also similar to CL0007, with 15 percent

of patients having standard of care positive margins in the validation set and 17 percent in the modified intent-to-treat population overall.

At this time, I'd like to invite Dr. Sue-Jane Wang to discuss the effectiveness results of these studies. Thank you.

FDA Presentation - Sue-Jane Wang

DR. WANG: Good afternoon. My name is Sue-Jane Wang, Deputy Director of Division of Biometrics I, Office of Biostatistics, Office of Translational Sciences, CDER, FDA. Following Dr. Masters' FDA part one clinical overview, I will provide a statistical study design and a regulatory review of the efficacy result of Lumisight used with Lumicell Direct Visualization System, DVS. I will begin by following the imaging drug Lumisight development flow and present Study 0006, then Study 0007. I will conclude with a summary of the statistical assessment of Lumisight efficacy.

In the Lumisight development program, Study 0006 was a feasibility study, single arm and multicenter, and to refine and lock down the

imaging detection algorithm used with the Lumicell DVS for detection of residual cancer tissue. Study 0006 used imaging data from 83 subjects with breast cancer receiving standard of care breast-conserving surgery to train the imaging detection algorithm by adding imaging data from 44 additional subjects after the initial training.

A total of 127 subjects of the extended training data set was used to finalize the imaging detection algorithm. At a high level, the detection threshold for a subject was calculated as the brightest contiguous feature, abbreviated as BCF factor, and multiplied this factor with the average of the smallest two BCF values of a subject. This BCF factor was 2.85 using 83 subjects and was 1.61 using 127 subjects. This lockdown prospectively refined the algorithm using a BCF factor of 1.61 and was validated in a non-overlapping data set of 103 subjects, and was then used in Study 0007, which is the primary study for providing efficacy of Lumisight.

The next two slides are the estimated

performance of Lumisight from the feasibility Study 0006. In this slide, I'd like to direct attention to the column labeled as "Validation Set Prospective Refined Algorithm." This column gives a semi-independent validation of a cross-validation study. As shown, the estimated detection rate was 8.7 percent with a lower bound of the 95 percent interval estimate of 4.1 percent. Study 0006 tissue-level estimate was 63.5 percent with a lower bound of the 95 percent confidence interval of 41 percent, and the tissue-level specificity estimate was 80.2 percent with a lower bound of 75.8 percent.

Dr. Masters has explained the design of Study 0007. Here, I will just highlight that although Study 0007 was a two-arm, randomized-controlled trial with the same patient population of Study 0006, the purpose of including this control arm in Study 0007 is very different from including a control arm in a typical two-arm, parallel arm, randomized-controlled trial. Here, the purpose of randomization is to minimize the

potential of bias from surgeons under-calling during his or her standard of care breast-conserving surgery. The relevant design feature of such a two-arm controlled trial is essentially an intrapatient controlled design.

All patients received the Lumisight injection. All patients received the standard of care breast-conserving surgery procedure regardless of whether they were randomized to the active arm or the control arm. Then only after the standard of care breast-conserving surgery is completed for all the subjects, the randomization assignments are revealed to surgeons, and the Lumisight-guided shave is only performed in the active arm, sometimes referred to as a device arm. Thus, for a given subject, the interests are the outcome of the standard of care breast-conserving surgery performance that was before Lumisight-guided shave and the Lumisight performance after the standard of care breast-conserving procedure.

The three co-primary efficacy endpoints in this controlled Study 0007 are the same as that in

the uncontrolled feasibility Study 0006 after the estimation learning process. For the controlled trial, the success threshold of each efficacy endpoint was prespecified; for P1, patient-level residual cancer detection rate, the prespecified threshold was 3 percent; for P2, tissue-level sensitivity, 40 percent was the prespecified threshold; and for the P3 tissue-level specificity, the prespecified threshold was 60 percent.

The sample size planning for Study 0007 is a little complicated. The feasibility study provided some reference in planning Study 0007, targeting success for the three co-primary efficacy endpoints. The sponsor noted that it is uncertain in translating the number of reference standard positive tumor tissues at the tissue level to the actual number of subjects at the patient level, so as a result, the study pursued a so-called event-driven design.

It was postulated that enrolling approximately 268 subjects would allow targeting 70 reference standard positive tumor tissues for

tissue-level sensitivity estimates, and adding this 10 to 1 randomization, the estimated total number of subjects would be approximately 310 subjects. In a later protocol amendment, the sponsor included a planned maximum number of subjects, which was 450. In the event-driven study design, the Data Safety Monitoring Board was charged to monitor the enrollment until 70 standard reference positive tumor tissues are collected to recommend the completion of Study 0007 accrual.

As shown at the upper-left corner of the slide, the DSMB recommended a completion of study accrual on September 15, 2021, when 69 standard of reference tumor positive events were reached at the database lock. Of the 406 subjects that received Lumisight, 14 subjects withdrew from the study after Lumisight injection but prior to study randomization. Among these 14 withdrawn subjects, seven were due to adverse events, and those adverse events of safety concerns are those with hypersensitivity reaction, at the bottom, three of them, and the anaphylactic reaction, one of them.

What's listed -- see the bottom right text in red -- are those with specific AEs that failed to complete a Lumisight injection. So if one adopts the intent-to-treat principle, these 14 subjects that received the drug should be included in the efficacy analysis. In Study 0007, the modified intent-to-treat subjects, excluding the 14 subjects, which will result in a total of 357 subjects in the active arm, the sponsor reported that the efficacy was based on the modified intent-to-treat subjects.

The results of the first co-primary efficacy endpoint, patient-level removal of residual cancer in the mITT patients, are shown in this slide, where residual cancer was confirmed by postoperative histopathology of surgical specimen, which was explained by Dr. Masters earlier. The estimated patient-level residual cancer detection rate was 7.6 percent.

Specifically, 27 out of the 357 patients had residual cancer found in at least one Lumisight-guided shave in the mITT patients, all

were based on level 1 standard of reference. This proportion becomes 7.3 percent using the intent-to-treat patients, including the 14 subjects who early withdrew from the study. Note that the lower bound of the 95 percent confidence interval using either the ITT patient set of 4.9 percent or the mITT patient set of 5 percent both exceeded the prespecified threshold of 3 percent. This first co-primary efficacy endpoint of patient-level residual cancer detection rate performance was similar between Study 0006 and Study 0007. See the circled interval estimates.

This slide shows the results of the second and third co-primary efficacy endpoints, namely tissue-level diagnostic performance for Study 0007. From the last row, the lower bound of the 95 percent confidence interval for the tissue-level sensitivity was 36.4 percent, which is less than the prespecified threshold of 40 percent; whereas the lower bound of the 95 percent confidence level for tissue-level specificity exceeded the prespecified threshold of 60 percent.

Here is a side-by-side view of the tissue-level diagnostic performance between Study 0007 and Study 0006. From the statistical review of the three co-primary efficacy analysis results of Study 0007, below we discuss each endpoint. First, patient-level detection of residual cancer varied among the 14 clinical sites. The aggregated summary yielded a lower bound 95 percent confidence interval estimate of approximately 5 percent, which exceeded the prespecified 3 percent threshold. Secondly, the sponsor used the GEE, generalized estimating equation, approach, accounting for the correlated tissues within a patient to estimate tissue-level sensitivity and tissue-level specificity, as shown in the row labeled as GEE approach.

The FDA performed a sensitivity analysis without adjusting the correlation among tissues in a patient. The results are shown in the row labeled as "Unadjusted Approach" to better understand the impact of correlation. It turns out the tissue-level sensitivity and tissue-level

specificity estimates from the two approaches appear similar, suggesting that, on average, the correlation among tissues in the patient is generally low. From the sample study obtained in Study 0007, we found that the observed tissue-level estimated prevalence is only about half of the planned prevalence, and that is the 2.9 percent observed as a tissue-level estimated prevalence versus 6.4 percent planned.

It has been mentioned the proposed indication for Lumisight is to be used as an agent for intraoperative detection of cancerous tissues during lumpectomy surgery. When adding up the concordance between the Lumisight imaging results and the standard of reference histopathology results, it gives the tissue-level accuracy, which is not a prespecified tissue-level efficacy endpoint.

This summary measure of at least 82.6 percent lower bound appears to suggest tissue-level diagnostic performance appears to be better than 50 percent chance accuracy, which in

turn might support the patient-level detection as an agent used.

Of the secondary efficacy endpoints, Dr. Masters mentioned two of them are included in the statistics presentation. This slide shows patient-level imaging performance. First, to derive a patient-level imaging performance from tissue-level imaging performance, there are multiple ways, but they should be prespecified.

Here, FDA explored two possible ways in selecting patient-level imaging status using the first status on a priority list that matches at least one tissue-level imaging status. One way uses the priority list on the table, the first row, that true positive takes the priority over the false negative, false positive, then true positive. The other way, the second row, uses the priority list of false negative followed by true positive, false positive, then true negative.

Shown in this table using either priority list, the estimated patient-level specificity is the same. Using a true positive as a priority over

false negative will naturally result in a higher patient-level sensitivity. In contrast, using false negative as a priority over true positive will result in lower patient-level sensitivity. By the very nature of the classification priority, both are important in our view.

Because there were only 69 tissue-level positive tumor tissues, but over 2,000 tissue-level negative tumor tissues, the priority sequence here has a larger impact on patient-level sensitivity estimates, but it has less impact in the accuracy summary measure, which shows a slightly better than chance accuracy with either priority list.

Another secondary endpoint is conversion rate. A patient is considered a converter if her pathology-positive margin after standard of care breast-conserving surgery resulted in the pathology negative margins following therapeutic shave. In Study 0007, there were 62 breast cancer patients out of 357 patients whose margin status after standard of care breast-conserving surgery was positive. This resulted in an estimated positive

margin after the standard of care procedure of about 17.4 percent with a 95 percent interval estimate of 13.6 percent and can be as high as 21.7 percent.

There were 9 converters mentioned by a few speakers previously. If the conversion rate is estimated among patients with a positive margin after standard of care breast-conserving surgery, this estimated conversion rate was 14.5 percent, which can be as low as 6.9 percent and as high as 25.8 percent from a 95 percent confidence interval estimate using the Clopper-Pearson method. When the conversion rate is estimated among the mITT patients, this estimate was 2.5 percent with a 95 percent interval bound of 1.2 percent and 4.7 percent.

To summarize, statistically, Study 0007 met the prespecified threshold on patient-level residual cancer detection efficacy endpoint and met the prespecified threshold on diagnostic tissue-level specificity, but did not meet the threshold on the diagnostic tissue-level

sensitivity. It is noted that none of the secondary endpoints were statistically powered. They provided information on patient-level imaging performance and conversion rate, among other endpoints, to be given in the next FDA part 2 clinical presentation.

Study 0006 was a feasibility study aimed to finalize the algorithm for detection at the tissue level and at the patient level. This feasibility study was an estimation study with no specific hypothesis test prespecified and was not a controlled study, but by locking down this imaging detection algorithm from Study 0006, the first co-primary efficacy endpoint, the estimated detection of patient-level residual cancer in Study 0006 appears similar to that observed in Study 0007.

This concludes the statistical consideration presentation. I appreciate the opportunity to share the FDA review finding, and now I'd like to invite Dr. Masters to continue part 2 of the FDA clinical presentation. Thank you.

FDA Presentation - Shane Masters

DR. MASTERS: Thank you very much, Dr. Wang.

I'd like to briefly discuss surgical specimen volumes in Study CL0007. The mean standard of care specimen volume was 89 milliliters in the modified intent-to-treat population, and this was similar between patients who had at least one therapeutic shave and patients who did not have any therapeutic shaves. Among patients who did have at least one therapeutic shave, the additional volume of specimen removed after standard of care surgery was approximately 22 milliliters on average.

The overall contribution of therapeutic shaves to the total volume of tissue removed was about 20 percent on average. Similar specimen volumes have been reported in studies' comprehensive shaves and available data suggests that surgical technique is more important to cosmetic outcomes than additional tissue volume, at least in the range that was reported in this study.

CL0007 included an optional breast

satisfaction survey using the breast-conserving therapy module of the breast cue developed at Memorial Sloan Kettering Cancer Center. Responses were obtained prior to surgery and through approximately 6 months after surgery. The number of patients completing the survey was roughly evenly divided between those who had no therapeutic shave and those who had at least one therapeutic shave, allowing comparison between patients with standard of care resection and additional tissue removed due to Lumisight. And as shown in the lower table on this slide, the mean scaled scores, which range from 0 to 100 with 100 indicating greatest satisfaction, were similar between the groups, accounting for a slightly lower score at baseline in participants with therapeutic shaves; however, interpretation of these results is significantly limited by the low response rate.

I'll now move on to discussion of some of the key safety results from the Lumisight development program. The safety database for the Lumisight development program included

790 patients. We defined the primary safety analysis population as patients with any cancer who received any amount of Lumisight at an intended dose of 1 milligram per kilogram, resulting in 726 patients. This population was chosen to reflect the to-be-marketed dose, and patients without cancer were excluded because they might have had less exposure to the cleavage products of pegulicianine. Ninety-seven percent of patients in the primary safety analysis population had breast cancer and 98 percent were female. The most commonly observed adverse event was chromaturia due to urinary excretion of the drug product or its metabolites, occurring in 85 percent of patients.

Eighty-eight percent of patients in the primary safety analysis population participated in either Study CL0006 or CL0007. These studies employed similar safety monitoring procedures. Standard preoperative, intraoperative, and postoperative monitoring was to be performed after administration of Lumisight. The applicant noted that the standard monitoring can vary across

institutions.

A final safety assessment was to occur at the first postoperative visit, which was timed according to standard of care rather than protocol. At this visit, patients were interviewed for adverse events and had safety laboratory blood sampling. In patients who had allergic reactions, additional laboratory analysis was to be performed in the form of histamine, total complement, and tryptase immediately and at 30 minutes after onset.

The adverse event of greatest concern was hypersensitivity. Hypersensitivity, as defined by the broad FDA medical query, was the second most commonly observed adverse reaction after chromaturia, occurring in 4.8 percent of the primary safety analysis population. When events were limited to those assessed as related to Lumisight by study investigators, 1.4 percent of patients had one or more hypersensitivity events; however, we do note that there were several complicating features for assessing causality. All patients in the major studies were exposed to

Lumisight, so there is no control group to estimate baseline rates of adverse events. Also, there are multiple other procedures and interventions that occur as part of standard of care on the day of breast-conserving surgery that can confound assessment. Among the hypersensitivity reactions, 4 patients, or 0.6 percent, had events adjudicated as anaphylaxis by FDA.

The other preferred terms identified by the hypersensitivity FDA medical query are shown on this slide. The most common preferred terms were rash of some form or pruritus. Events that occurred on the day of Lumisight injection are also shown on this slide as a way to highlight events that might be more likely related.

Notably, all the events that were characterized as anaphylaxis occurred during or immediately after injection of Lumisight, all required medical therapy in some form, and three resulted in study discontinuation. Among the other hypersensitivity reactions, 3 percent were considered severe by the investigator, at least

6 percent had onset during Lumisight injection, and 6 percent resulted in study discontinuation.

So I'll summarize the presentation from FDA's perspective on efficacy and safety results. Removal of additional cancer after standard of care surgery, as performed in the CL0007 study and as indicated in the draft prescribing information for Lumisight, could be considered clinically meaningful through potentially reducing rates of reoperation and possibly tumor recurrence. The observed tissue-level sensitivity and specificity in CL0007 for removing additional cancer provide a direct assessment of the diagnostic performance of Lumisight and demonstrate better than chance accuracy, which support the patient-level cancer removal co-primary endpoint. These endpoints are consistent with the FDA imaging drug guidance for providing evidence of effectiveness for disease detection indication. For the proposed indication, evaluation of patient outcome endpoints would typically not be required.

Among the secondary efficacy endpoints, we

note that nine of the 62 patients who had margins positive for cancer following standard of care surgery converted to all negative margins after Lumisight-guided shaves. All nine of these patients had detection of all their positive margins that were left by standard of care surgery; however, eight of these nine patients did not have cancer identified in a Lumisight-guided shave. Among the remaining 295 patients who had all margins negative for cancer after standard of care surgery, additional cancer was removed by Lumisight-guided shaves in 19 patients.

The major risk of the product is that of anaphylaxis and serious hypersensitivity reaction. Anaphylactic reactions occurred in four of the 726 patients in the safety primary analysis population. The perioperative setting of administration and appropriate labeling are expected to reduce the incidence of severe adverse outcomes in patients who do have anaphylaxis, though of course the risk of anaphylaxis itself would not be affected by those measures. A postmarketing requirement study

and enhanced pharmacovigilance are expected to provide further characterization of the risk of anaphylaxis.

At this time, I'd like to pass the podium to Dr. Anil Rajpal who will discuss uncertainties in the safety assessment and risk management considerations for Lumisight.

FDA Presentation - Anil Rajpal

DR. RAJPAL: Good afternoon. My name is Anil Rajpal. I'm the Deputy Director for Safety in the Division of Imaging and Radiation Medicine. I will talk about risk management considerations. I'll first be discussing the safety concerns and uncertainties, then possible risk management approaches and limitations, including labeling, a postmarketing requirement or PMR safety study, enhanced pharmacovigilance or EPV, and risk evaluation and mitigation strategies, or REMS, with elements to assure safe use or ETASU. Finally, I will summarize the key points.

The safety concerns of interest are summarized here. The incidence of hypersensitivity

reactions, including anaphylaxis, are shown. Anaphylaxis cases occurred during or immediately after administration. There are some uncertainties in the data that are important to consider. For example, the limited sample size of 726 makes it difficult to get accurate estimates of the incidence of anaphylactic reactions. There was not an unexposed control group, and this was in the setting of preoperative confounders. There is limited information on how patients were monitored following Lumisight administration in the clinical trials. The time frame for monitoring that should be recommended is not clear. The applicant proposes patients should be monitored for 15 minutes following the administration of Lumisight.

First, some background about why risk management is needed. Lumisight is intended to be administered to patients 2 to 6 hours before surgery and intraoperative imaging. The serious hypersensitivity reactions, including anaphylactic reactions, were observed in the preoperative

setting. These were during or immediately after the infusion, but the time to onset may vary with wider exposure. The time frame for monitoring that should be recommended is uncertain.

To manage these serious hypersensitivity reactions, including anaphylactic reactions, there's a need for monitoring and for immediate availability of trained personnel, emergency resuscitation drugs, and necessary equipment. We expect that the sites where this will be administered would have the appropriate monitoring personnel, drugs, and equipment should anaphylaxis occur during or immediately after the infusion, but we have some uncertainty about the level of monitoring and the availability of personnel, drugs, and equipment if events occur later in the 2 to 6 hour window before surgery.

This slide has the same information as the last two slides depicted graphically. Lumisight is intended to be administered to patients 2 to 6 hours before surgery. The anaphylactic reactions in the clinical trials occurred during or

immediately after the infusion, but the time to onset may vary with wider exposure. To manage these serious hypersensitivity reactions, including anaphylactic reactions, we want to ensure monitoring and immediate availability of personnel, drugs, and equipment that are needed. The time frame for when these reactions will occur is still not clear. We would like the advisory committee panel to comment on the recommended time frame for monitoring and for the availability of personnel, drugs, and equipment.

It's important that the Lumisight prescribing information, or PI, communicate the risk of anaphylaxis and other hypersensitivity reactions, the need to monitor patients, and the need to have appropriate personnel, medications, and equipment available. This would be done by warnings and precautions and a boxed warning. Note that this approach would only communicate the risk; it would not further characterize the risk. The Warnings and Precautions section is intended to identify and describe a discrete set of adverse

reactions and other potential safety hazards that are serious or otherwise clinically significant because they have implications for prescribing decisions or for patient management.

This slide shows the language being considered for warnings and precautions. I have highlighted the key features. The first paragraph identifies the risk of anaphylactic reactions and the timing. These can occur during or following administration. The second paragraph gives the frequency. Four of 726, or 0.6 percent, of patients in studies had anaphylaxis events. It also describes the signs and symptoms.

The third paragraph gives the risk factors. It states that three out of four patients that experienced anaphylaxis did not have a history of hypersensitivity reaction to contrast media or products containing polyethylene glycol, or PEG, in the clinical studies.

Management is described in the fourth paragraph. Emergency resuscitation drugs, equipment, and trained personnel must always be

available. All patients should be monitored for hypersensitivity reactions using symptom reporting, direct observation, and vital sign measurements. If a hypersensitivity reaction is suspected, the injection should be discontinued and appropriate therapy should be initiated.

A boxed warning is ordinarily used to highlight for prescribers one of the three situations shown here. In bold red text are the portions that may be relevant to this product: the first situation, adverse reaction so serious in proportion to the potential benefit that it is essential that it be considered in assessing the risks and benefits of using the drug; or the second situation, serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug -- three examples are careful monitoring, addition of another drug, or managing patients in a specific manner -- or the third situation, FDA approved the drug with risk evaluation and mitigation strategies, or REMS, with elements to assure safe use or ETASU.

This slide shows language being considered for a boxed warning. This would communicate the risk. I have highlighted the key features. The first paragraph identifies the risk and provides the expected time frame and observed frequency of anaphylactic reactions. Management is described in the second and third bullets.

There are complementary approaches for risk management being considered: the postmarketing requirement or PMR safety study; enhanced pharmacovigilance or EPV; and risk evaluation and mitigation strategies, or REMS, with elements to assure safe use or ETASU. I will be describing these approaches in more detail in the following slides, including their limitations.

First, a PMR safety study, if it is adequately designed and executed, it could provide real-world experience describing incidence of serious hypersensitivity adverse reactions and time to onset of hypersensitivity adverse events. A limitation is that it would not mitigate the risk. Next, enhanced pharmacovigilance or EPV

considerations, this is a potential approach to further characterize a known risk, in this case hypersensitivity reactions, including anaphylaxis.

First, some background about enhanced pharmacovigilance. FDA may request the applicant to summarize and assess interval and cumulative data for adverse events of interest, in this case, hypersensitivity reactions at a recurring frequency defined by FDA. FDA may also request the applicant to submit expedited 15-day individual case safety reports for certain labeled adverse events of interest that are not otherwise required by regulation to be submitted as 15-day reports.

The limitation of this approach is that enhanced pharmacovigilance would not directly reduce the risk of hypersensitivity, but it may foster more timely submission of hypersensitivity-related safety information to FDA, and it may allow for a more rapid regulatory response if the observed reporting frequency, time to onset, or clinical severity of hypersensitivity reactions is greater than or different from what is

described in product labeling.

The last approach being considered is a REMS with ETASU. A REMS could be required if additional risk mitigation strategies beyond labeling are necessary to ensure the benefits of Lumisight outweigh the risk, in this case anaphylaxis. If required, a REMS with ETASU for this product would restrict administration of Lumisight to healthcare settings that are certified in the REMS.

As part of the certification, healthcare settings would be required to have policies and procedures to support monitoring and management of anaphylaxis. Each patient using the drug would be subject to certain monitoring during the period of greatest risk. Patients would be counseled about the risk and symptoms of anaphylaxis and what to do if symptoms occur. This type of REMS would impose administrative burden on the healthcare system.

The agency is considering each of the risk management approaches. We will consider the advisory committee's advice in regulatory decisions. To summarize, labeling would mitigate

the risk through communication of the risk but would not further characterize the risk. A PMR can further characterize the risk, incidence, and time to onset of anaphylaxis and hypersensitivity reactions if the study is well-designed and executed, but it would not mitigate the risk.

Enhanced pharmacovigilance may help to further characterize the risk and may allow a more rapid regulatory response if case reports provide new information not in the labeling such as frequency of reactions, time to onset, or clinical severity of reactions, but it would not directly reduce the risk. A REMS with ETASU would restrict administration to settings with policies and procedures to support monitoring and management of anaphylaxis, but would impose administrative burden. Thank you.

Clarifying Questions to the FDA

DR. ROYAL: Now we will take clarifying questions for the FDA presenters. Please use the raise-hand icon to indicate if you have a question and remember to lower your hand by clicking the

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

Cynthia Pearson?

MS. PEARSON: Thank you. This is Cynthia Pearson, acting consumer rep. My first question is to the last speaker who mentioned REMS as a possibility. Are there any other imaging drugs that are under a REMS right now?

DR. HOFLING: Thank you for that question regarding other imaging drugs under a REMS. I'll ask Dr. Anil Rajpal to come back to the podium.

DR. RAJPAL: So there are three products subject to a REMS that include elements to assure

safe use, or ETASU, and there are several products associated with risk of anaphylaxis that are -- I'm sorry. I wanted to clarify, there are three products subject to a REMS that include the elements to assure safe use, where the risk is anaphylaxis, and there are several products that have the anaphylaxis in the labeling without a REMS.

I'd like to ask one of my colleagues to help answer this question, Dr. LaCivita.

DR. LaCIVITA: Hi. Cynthia LaCivita. So there are no imaging products currently that are approved with the REMS or subject to a REMS. There are other products that are approved that have anaphylaxis, and they are approved with REMS, and the incidence of anaphylaxis is somewhat higher than it is for the product being discussed today.

Does that answer your question, sir?

MS. PEARSON: Yes. Thanks for that extensive answer. In the interest of lunch, I'll pass on my second question, so that's all for me. Thanks.

DR. ROYAL: Thank you.

The next question is from Dr. Rosenthal.

DR. ROSENTHAL: Thank you. I had a question about the environment that this is administered almost always has resuscitation equipment. I'm just curious. You say it's an increase to administrative burden, but I think the amount of drugs given in general in those locations, it seems like as long as the patient is awake and is in the PACU, that the resuscitation equipment, I'd be surprised if it wasn't available even at the outpatient ASEs [ph]. Do you know that that's an increased burden or not?

DR. HOFLING: Thanks for that question regarding the burden of a REMS. I'll bring Cynthia LaCivita back to the podium.

DR. LaCIVITA: Hi. It's Cynthia LaCivita, FDA. The administrative burden associated with a REMS typically has to do with the certification requirements, and then ensuring that those processes and procedures are in place. We do recognize that most of the facilities that would be

administrating this product would have trained personnel, emergency equipment, and other things on hand. Thank you.

DR. ROYAL: Dr. Xiong?

DR. XIONG: Alright. So I have maybe two questions, one to Dr. Wang, the other to Dr. Masters. I understand Study 0006 and Study 0007 are a bit different, especially in the lack of control arm, but so far I think we don't see any control arm data because it's a small sample size, which I understand. But my question is, given a lot of similarities between Study 0006 and Study 0007, is it possible to combine those two study data to do some kind of meta-analysis so that we can have a better estimate to sensitivities, specificity of tissue-level, as well as maybe patient-level cancer rate?

I know this is probably having some [indiscernible - 4:49:18] in the sense that you're mixing a control trial with a large observational study, but given that the sample size is really small, I thought that may be something that we can

look into, and I wonder whether we have done.

DR. HOFLING: Thank you for that question regarding combining the trial data for a meta-analysis. I'll ask Dr. Sue-Jane Wang to comment on that.

DR. WANG: Thank you for the question. This is Dr. Sue-Jane Wang from the FDA. Regarding meta-analysis, this is always a statistical approach that one can do after the fact that the study has done and tried to combine, but the FDA encourages that kind of meta-analysis is generally for safety, not for efficacy, and also, we will want the meta-analysis to be prespecified the approaches of combining, et cetera. The reg so far, we look at the basis of independent studies, so for efficacy/evidence setting, we will be looking at the two studies separately.

In terms of combining the control arm, as mentioned by many of the speakers, the control arm here really isn't for any comparison at all, although they receive the drugs, and then they receive the standard of care surgery, but that's

the end of that procedure for the control arm. The assessment really is an intrapatient assessment. You look at the patient's imaging performance at the end of the standard of care breast-conserving surgery before the Lumicell-guided shave versus the Lumicell performance after the standard of care breast-conserving surgery. So that's the kind of comparison of interest in such a study design.

DR. XIONG: Great. Thank you. I didn't really mean to involve the control arm. I think your answer is very clear in terms of the FDA's reservation of combining data from different studies for efficacy, which I understand.

Alright. So maybe this next question is to Dr. Masters. I think you mentioned, if I recall correctly, on your slide 67, 191 patients have no therapeutic shaves. Is that an accurate statement? I just want to confirm that's the number.

DR. HOFLING: Thank you. I will bring Dr. Masters up.

DR. MASTERS: Hi. This is Shane Masters. If we can pull up backup slide 12, please; 166

patients had at least one therapeutic shave and 191 had no therapeutic shaves. That's correct.

DR. XIONG: Right. So those people actually have no Lumicell data.

DR. MASTERS: They have Lumicell imaging data. All of their orientations were imaged after the standard of care surgery was complete, and because the imaging did not show any positive results, there were no therapeutic shaves in those patients.

DR. XIONG: Great. Thank you, Dr. Masters.

DR. MASTERS: Okay. Thank you.

DR. XIONG: Thank you. I have no further questions.

DR. ROYAL: Okay. Dr. Vasan?

DR. VASAN: Hi. Neil Vasan, Columbia University. I have two questions. The first has to do with effectiveness. On FDA slide 61, I noticed that when the diagnostic performance was assessed with an unadjusted approach, that that lower bound, that 36.4 percent, went up to 38 percent, and I know that from the background

materials, I believe in the earlier phase trials, the sensitivity was 38 percent.

So my first question is just, that 40 percent number, was that just like a rounding up or was there some reason that 40 percent was chosen over 38 percent? And this just has to do with effectiveness in that lower bound.

DR. HOFLING: Thank you for that question regarding the lower bound for the efficacy endpoint of effectiveness, and I'll ask Dr. Sue-Jane Wang to comment on that.

DR. WANG: Sue-Jane Wang again. In terms of the threshold of 40 percent, this was proposed by the sponsor, not proposed by the FDA, and their argument was using the standard of care pathology data from Study 0006 to select that threshold that they presented. And during the development stage, FDA did agree with that prespecified threshold. It wasn't, after looking at the result, to say that this is the threshold. Perhaps the sponsor can reiterate how they chose the threshold.

DR. FERRER: This is Jorge Ferrer again from

Lumicell. Yes, it was a rounding up approach, where we look at the 38 percent from the pathology margin assessment from the prior study, and we round that up to 40 percent to establish the lower bound for sensitivity.

DR. VASAN: Okay. Yes. Just to clarify, that was really just a rounding up; it wasn't some sort of plus 2 percent that was derived somewhere else.

DR. FERRER: No, rounding up.

DR. VASAN: My question is based on FDA slide 103, the REMS with ETASU. I guess I'm just trying to get a little more clarification on the statement, "monitoring/management" of anaphylaxis. As someone else previously mentioned, these procedures would be done at either a hospital or an outpatient surgical site where standard anaphylaxis monitoring would occur, but does that mean having an ICU?

Is there any more color that the FDA can provide about what exactly that means in terms of monitoring and management? Is this similar, for

instance, to just getting chemotherapy in an outpatient facility where many drugs have a risk of anaphylaxis and we monitor with corticosteroids and antihistamines, et cetera, epi if needed, transferred to an ICU, or is this more of an insight monitoring management?

DR. HOFLING: Thanks for that question regarding the level of monitoring for the adverse reactions. I'll ask doctor Rachel Bean to comment on that.

DR. BEAN: Hi. Rachel Bean, allergist with the Division of Pulmonology, Allergy, and Critical Care at FDA. Thank you for the question. The monitoring procedures that we are advising would be eliciting symptoms, having observation and vital signs, and not necessarily specifying beyond that. We would have a goal of being able to detect potential hypersensitivity or anaphylaxis reactions with those monitoring guidelines in place, so we would welcome any input from the committee today about if there are specific measures that you would recommend. So I hope that answers your question.

Thank you.

DR. VASAN: Thank you.

DR. ROYAL: Dr. Leitch?

DR. LEITCH: I just wanted to clarify, on the slide, I think it's 76, that talks about the benefit and the primary efficacy endpoints, it seems that the standard for the FDA does not require -- these imaging devices do not require the patient-level efficacy; that the tissue-level efficacy is sufficient. Certainly, the patient-level issue has been brought up in this meeting, but for FDA criteria, what has been submitted is acceptable.

DR. HOFLING: Thanks for that question regarding the acceptability of the sensitivity and specificity endpoints, particularly with regard to patient level versus tissue level. I'll just start with some comments on that, and perhaps my other FDA colleagues can join afterwards.

Our point was that some determination of sensitivity and specificity have historically been sufficient for supportive effectiveness of a

disease detection claim. Whether that's at patient level or or tissue level, I don't think there's a firm guideline there. From my perspective, it's always best to start looking at sensitivity and specificity at the most granular level; in this case it would be tissue level. If you don't have a better than chance performance, there's really no point to proceeding to patient level. So in some ways, tissue level, the very granular level of sensitivity and specificity, you could argue are most important.

Now, patient-level sensitivity and specificity, that's maybe more applicable and more moving towards the realm of of utility, so it's also important. One challenge to evaluating patient-level sensitivity and specificity is that you need a method to convert the granular data, the tissue-level data, to patient-level data, and that's difficult, and it can sometimes be arbitrary on how you do that. You have to have some method to do it, and you notice that we explored two different methods of doing that, but there are many

other methods.

It also becomes very challenging when there are multiple inputs, so the more inputs that you have at a granular level that go into the patient-level metric, it just becomes more difficult to choose that algorithm and to set it up; and here we have six inputs for patient, which makes interpretability of the patient-level results difficult. So I think whether or not we rely on patient level or tissue level, it depends in part on the data that we're looking at, the trial design that we're looking at, the clinical context.

So just to sum up, we do want to look at sensitivity and specificity in some fashion, and historically we've been pointing that out as the historical ability for that to be sufficient to support disease detection, specifically to contrast or to point out that further evaluation of clinical outcomes has typically not been necessary.

I'm sorry. I hope that answered your question. I don't know if any of my FDA colleagues have additional input.

DR. LEITCH: It seems like it's kind of either/or, huh?

DR. HOFLING: Yes. I think it depends -- if I was pressed, I think historically we've relied more often -- if you look through our labels for imaging drugs, you'll more often see patient-level sensitivity and specificity reported. I think in some of our more recent approvals, we have both. I think in this particular setting, again, because of the six inputs that go into each patient's patient-level endpoint, that presented a greater challenge than usual at interpreting patient-level sensitivity and specificity.

DR. LEITCH: Okay. Thank you.

DR. ROYAL: Dr. Jacobs?

DR. JACOBS: Paula Jacobs, NCI. This is a question regarding the REMS. Are there any drugs with this level of hypersensitivity that are administered in such a controlled setting that have a REMS? I mean, I know about drugs that are typically outpatient, so obviously you'd want to train them, but I can't imagine that people

monitoring patients pre-op need extra training in dealing with adverse events. This seems a little like overkill.

DR. HOFLING: Thank you for that question regarding the necessity of a REMS in the perioperative setting. I'll ask Dr. LaCivita to come up.

DR. LaCIVITA: Cynthia LaCivita, FDA. So the products that are currently approved with a REMS started in an inpatient setting, and then there are maintenance drugs that are used outpatient, so these are patients that are using these products in the home setting. At this time, we don't have any REMS to identify to mitigate risks of anaphylaxis in a hospital setting, so you're correct. Thank you.

DR. JACOBS: Thank you. That's all the questions I have.

DR. ROYAL: Dr. Skates?

DR. SKATES: Hi. Steven Skates from Massachusetts General Hospital. Thank you for this presentation from the FDA. It was quite helpful.

I'd like to weigh in on the the patient-level versus the tissue-level sensitivity and specificity. In my judgment, safety and efficacy, which those two sensitivity and specificity partially address, both of them need to be the primary analysis rather than the secondary analysis, and needs to be at the patient level because the decision is at the patient level. Either you use Lumicell for the patient's operation or you don't. You don't take individual decisions any more granular than that. And therefore, safety and efficacy that FDA's mandated to assess should be at the patient level because that's where the decision is at.

So with that in mind, I'd like to ask Dr. Sue-Jane Wang about the patient-level performance on slide 62 compared to the tissue-level performance on slide 61. The sensitivities are not that different, tissue level to patient level, so that's not so much a concern; in fact, that's reaffirming that the patient-level sensitivity is in fact a bit higher. My concern is

with the specificity, and one minus a specificity is a false positive rate. So at the patient level, that false positive rate is quite high and that is my concern.

In fact, if you look at the estimates of the patient-level specificity, not only is the lower 95 percent confidence limit less than that predefined 60 percent, and I realize that 60 percent was chosen for the tissue level, but nonetheless, both the patient-level specificity point estimate, 57 percent, and the lower 95 percent confidence intervals for both rows on slide 62 are all less than the 60 percent, and that leads me to a great concern that this false positive rate -- and Dr. Ferrer in his slides listed the risks as the false positives plus the serious hypersensitivity and anaphylaxis.

The false positives have simply disappeared from the safety aspect of the FDA's presentation, and it's reflected; and my concern is that that high level of false positive rates that's indicated at the patient-level analysis is simply lost, and

that information is not on the product insert that will alert patients and surgeons about that high level of false positive rate.

So I would like to hear from Dr. Sue-Jane Wang about the choice of whether it's possible to make the patient level the primary analysis here because I think that is crucial in assessing safety and efficacy for patients.

DR. HOFLING: Thank you for that question, again, regarding patient-level versus tissue-level sensitivity and specificity. I'll ask Dr. Sue-Jane Wang to come up to comment. I'll just note while she's coming up, we have a co-primary endpoint of cancer removal or cancer detection rate, which is at patient level, and we do have some precedent in co-primary endpoints, combining endpoints that are both patient level and a more granular level.

DR. WANG: Thank you, Dr. Skates, for the question. It is a very difficult question. Between centers, sometimes patient-level sens [ph] and spec are considered to be more important than the tissue-level sens and spec. But given what

Dr. Hofling had also mentioned, the six inputs from the orientation level to come up with a patient level, it can be challenging; however, your point is well taken. In this case, patient-level specificity doesn't matter how you prioritize the false positive or the true positive versus the false negative; that patient-level specificity does not change, and the lower bound was just a little over the 50 percent, which is 51 percent in this case.

But as a study design, we generally follow the principle of prespecification and agree upon that the endpoints, in this case, was thought that the diagnostic performance at the tissue level is really the first gate that needs to demonstrate the benefit, so agree upon the co-primary efficacy endpoint includes the tissue-level sens and spec rather than the patient-level sens and spec. And we did look into this patient-level sens and spec and provided you some information there for the support possibly, but I'm not certain that, in this case, we should bring that up to become the primary

or the co-primary in this setting.

Thank you, and I believe maybe others will chime in from the FDA side.

DR. SKATES: It would be great to hear about the false positives not being mentioned as part of the safety. Thank you.

DR. HOFLING: I'll start with comments on that. We do agree that we need to pay attention to false positive rates, particularly for optical imaging agents, and this is no exception, so your comments are definitely noted. We would just mention -- not to downplay the significance of a false positive during a lumpectomy, but false positives, you do need to think about false positives in terms of the clinical context.

For instance, a false positive when we're resecting glioma, we would think about that much more heavily than a false positive when we are doing a lumpectomy surgery. That being said, I don't mean to minimize the impact of the false positives and it's something that we need to consider.

Are there other comments from the FDA?

DR. SKATES: Any chance of that making it on to the safety document or --

DR. HOFLING: The labeling.

DR. SKATES: -- the labeling.

DR. HOFLING: Yes, that's definitely an option. In fact, most of our imaging drugs that are approved for disease detection tend to have a fairly standard warning for what we call misdiagnosis for false positives and false negatives. So yes, I imagine that would be included in labeling. We were planning on including that and, yes, certainly, that's the plan.

DR. SKATES: Great. That's really helpful to hear. Thank you very much.

DR. HOFLING: Sure.

That's the end of my question.

DR. ROYAL: Thank you.

Well, I don't see any more raised hands, so we can now break for lunch. We'll reconvene at 2:30 Eastern Time. Panel members, please remember

that there should be no chatting or discussion of meeting topics with other panel members during the lunch break. Additionally, you should plan to reconvene at around 2:20 to ensure you're connected before we restart at 2:30 PM. Thank you.

(Whereupon, at 1:42 p.m., a lunch recess was taken, and meeting resumed at 2:30 p.m.)

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

(2:30 p.m.)

Open Public Hearing

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

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

Likewise, FDA encourages you, at the

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

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, please unmute and turn on your webcam. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you represent for the record. You

have 5 minutes.

DR. HARNESS: Good afternoon. I'm Dr. Jay Harness. My financial disclosure is that I chair the Lumicell Data Monitoring Safety Board for which I receive honorary payments. I have no other financial disclosures. I am a University of Michigan educated and trained general surgeon. I'm also a past president of the American Society of Breast Surgeons and Breast Surgery International. Most recently, I was a clinical professor of surgery at the University of California Irvine.

As I'm sure all of you know, breast conservative surgery emerged in the early to mid 1980s as an acceptable alternative to total mastectomy for the treatment of breast cancer. I've been focused on breast-conserving surgery since 1985 when I was appointed the first director of the University of Michigan Multidisciplinary Breast Center.

We knew from the very beginning that there were two major issues we faced in breast-conserving surgery. The first was obtaining microscopically

negative surgical margins and the second was preserving or improving the cosmetic outcome from our surgical procedures. Over the past 20 years, we have made great strides in improving cosmetic outcomes utilizing oncoplastic surgical techniques. Progress has been, however, slower in developing a real-time technology for assessing microscopic margins in the operating room.

This morning, you heard from many of my nationally recognized breast surgery colleagues. For my part, as I said earlier, I am the chair of the Lumicell Data Safety Monitoring Committee for the trials that were presented to you this morning. The Data Safety Monitoring Board is also known as the DSMB. We're responsible for routinely reviewing and evaluating cumulative safety data and assessing participant safety, study conduct, study progress, and helping to determine if there are any new risks to study participants based on our study data reviews.

The DSMB consisted of myself, also an independent biostatistician, and a breast surgery

colleague, Dr. Shawna Willey, who I believe will be speaking next. The DSMB has had several scheduled meetings, but we also held ad hoc meetings when any serious hypersensitivity events were reported or when a non-serious hypersensitivity event occurred. We took the safety of the participants very seriously and we were extremely thorough in reviewing the study data in great detail. At no point -- and I want to repeat, at no point -- during the studies were the reports of adverse events occurring at an unacceptable rate or at a severity level that made the DSMB concerned about allowing the continuation of enrollment into the studies.

In my opinion, the Lumicell technology is needed. Patients, surgeons, and the overall healthcare system will benefit from the use of this drug and device. The benefits -- and I want to repeat this, the benefits -- far, far outweigh the risks. I hope that as a committee, you choose to help get this technology into the hands of breast surgeons so that we can help and improve patient

outcomes. Thank you very much for the privilege of your time.

DR. ROYAL: Speaker number 2, please unmute and turn on your webcam. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you're representing for the record. You have 5 minutes.

DR. BLOOM: Okay. My name is Diane Bloom, and I live in Chapel Hill, and a little bit about myself is that I have a doctorate in human development and psychology and a master's degree in public health. I'm a qualitative researcher in the healthcare field, so I conduct focus groups and in-depth interviews with patients and physicians on a variety of different topics. I'm also an adjunct assistant professor at the University of North Carolina, and I'm speaking today because I'm a patient, a breast cancer patient, who had three re-excisions.

In 2015, I found a lump on my right breast, which turned out to be invasive breast cancer. After preliminary tests, my surgeon scheduled me

for a lumpectomy. The confirmation of the diagnosis and the upcoming surgery were extremely stressful for me. Although I remember my surgeon mentioning the percentage of time to have a second surgery and for me to get clean margins, I for some reason assumed that I wouldn't be among the group of women who needed re-excision.

The days leading up to the surgery were really nerve-wracking for me. I dreaded having surgery and risking complications, but the surgery went well, and after I woke up in the recovery room, I felt a tremendous sense of relief that it was all over, or so I thought. But when I had my appointment with the surgeon the next week and the pathology results had come back, I was expecting that everything would be fine, and it didn't even occur to me that I would need a second surgery. But when my surgeon said she had to go back in to get cleaner margins, I was really disappointed because it had taken me so much effort to face the first surgery, and I just didn't know if I could build up the nerve to go in for a second surgery.

The first re-excision was then scheduled, and I spent a fair amount of my time just worrying and dreading having to go through another surgery, but, really, there was no choice because I wanted to save my breast. I did have the second surgery. It was shorter and easier to recover from, but then when I had the next appointment with my surgeon the next week to go over the pathology report, it was very stressful before just to find out if the margins were really clear, and my husband was also stressed. So I found myself teetering between hope and despair before the appointment that day, worried that I might ultimately have to have a mastectomy if we couldn't get clean margins.

When I got to my appointment, I found out the margins still weren't clean enough, so I had to go back for another re-excision. The second re-excision surgery also didn't get the margins, but by this time, I was still disappointed but more resigned to go into surgery yet again for a third re-excision. My surgeon at this point arranged to have a runner that would go from the surgical room

where I was to run with my tissue sample across the street to the pathologist who was waiting and able to give a good idea during the surgery about whether we got the margins, and he thought that we did get the margins that time, and that was confirmed a couple days later on closer analysis; so it was a tremendous relief for me, but this was after having three re-excision surgeries.

Today, you're reviewing something that might have helped my surgeon avoid some of those three extra surgeries. Even if it provided just the smallest help to my surgeon for getting the margins, it would have been such a relief to me and to my family. I could have avoided so much stress, and so many sleepless nights and hospital visits, and recovery, and I could have just been living my life versus living in a state of fear and worry.

Please remember my story today as you make your decision, and there are thousands of other women just like me out there who also need you to remember them today. Thank you very much.

DR. ROYAL: Speaker number 3, please unmute

and turn on your webcam. Will speaker number 3 begin and introduce yourself? Please state your name and any organization you're representing for the record. You have 5 minutes.

DR. MONTES: Hello. My name is Dr. Jennifer Montes. I am reading this on behalf of Karen Maness. I will be speaking later on behalf of myself, so I will read her testimony.

"Hello. My name is Karen Maness. I am 57 years old and live in Lexington, North Carolina. I've been blessed with a wonderful husband for 29 years and have 5 children and 14 grandchildren. I love supporting my family in everything they do.

"I was diagnosed with stage 1 breast cancer in December of 2019. In January of 2020, I went to Dr. Carr's office to see what my next steps are going to be. After reviewing information about the Lumicell trial with Dr. Carr and my family, I decided to participate. I wanted to give myself and Dr. Carr the best chance of getting all the cancerous cells we could during my surgery, and maybe my participation in the trial could help

other women like me in the future, maybe even my own girls one day.

"My surgery was scheduled for late January of 2020. On the day of surgery, Dr. Carr went over the side effects that could happen with Lumisight and made sure I felt comfortable before we got started. After he administered the Lumisight, I started to feel nauseated, which was a side effect that Dr. Carr had explained to me. The specialist who was there with Dr. Carr took vials of my blood every 15 minutes. After about 30 minutes, I felt better and was able to have my surgery. Dr. Carr removed my tumor, and thanks to Lumisight, Dr. Carr was able to find and identify additional cancer cells and remove those, too. Without Lumisight, he may not have found those cells.

"Since my surgery in 2020, I have done 20 rounds of radiation and have been taking anastrozole. I have mammograms every year and they have not found any cancer cells. I've gone back to work part time at Christian School, take care of my grandkids after school, and volunteered to help

them with their sports and snacks. I believe Lumisight may have saved my life. It certainly helped Dr. Carr do the best he could do for me.

"Like I said earlier, I love supporting my family in everything they do. As you consider your decision today, I would ask you to remember my story and the thousands of women like me out there who love their families and are fighting breast cancer. They need an option like this that can help their surgeons do the best they can in helping them with that fight so they can be with the families that they love."

DR. ROYAL: Thank you.

Speaker number 4, please unmute and turn on your webcam. Will speaker number 4 begin and introduce yourself? Please state your name and any organization you're representing for the record. You have 5 minutes.

DR. DYESS: My name is Lynn Dyess, and I have no financial relationship at all with this entity. I am an academic surgeon. I'm a Professor of Surgery here at the University of South Alabama.

It's the only job I have ever had. I'm in lower Alabama. Many of my patients are from rural, underserved areas in lower Alabama. Many of my patients travel more than 100 miles each way to Mobile, seeking care for their breast cancers. Many of these patients, as well as from the local community that I serve, are from a lower social economic group. These patients, they deserve standard of care just as if they were in a big city, as if they were being provided at famous healthcare facilities.

The ability to participate in the Lumicell trial allowed me to offer these patients the opportunity from these underserved areas, these underserved patients, and to participate in breast cancer research just as if they resided in a larger community. The ability to evaluate their margins at the time of surgery with Lumicell will benefit these patients in the future if this agent is approved because of decreasing the times a second surgical procedure is required to evaluate the margins. Many times, if these patients require an

additional surgical procedure, the time to definitive care is prolonged; the return to surgery imposes additional trips to Mobile; financial burdens of the travel; and lost work days for the families providing transportation.

Oftentimes, re-excision results in more of a cosmetic deformity than clearing the margins at their initial surgical procedure, and there are times that patients in these areas will opt for a mastectomy simply because they cannot take the chance that margins might be too close that they might require additional surgeries. For numerous reasons, though, I think that Lumicell would benefit these patients.

In summary, Lumicell is a tool that will allow me as a surgeon for more precise surgery for my patients and better cancer operations for these underserved patients. I thank you very much for the opportunity to make my statement.

DR. ROYAL: Thank you.

Speaker number 5, please unmute and turn on your webcam. Will speaker number 5 begin and

introduce yourself? Please state your name and any organization you're representing for the record. You have 5 minutes.

MS. HUIE: Good afternoon. My name is Donna Huie, and I have no financial disclosure to make. I am 64 year years old, and I live in a small town called Walkertown, North Carolina, population 5,000, with my husband and our two dogs, Zoey [ph] and Sophie, who keep us active. I've had a 35-year career in healthcare in Winston Salem as a clinic administrator for a family medicine practice.

I was diagnosed with invasive ductal carcinoma in June of 2020 during the pandemic. I'd always gotten routine mammograms, as I felt they were important for women's healthcare. I was contacted and asked to come back in for a diagnostic mammogram and an ultrasound. At that time, I was not overly concerned, as I'd had to have repeat mammograms before. After the testing, I was asked to wait to speak to the radiologist. The radiologist was very reassuring but said a biopsy would be needed to rule out malignancy. I

had the biopsy and waited for the results.

During the lockdown, patients weren't allowed to come to the office for the results but were set up with phone calls. I have heard people use the phrase, "punch to the gut," but never grasped what that meant until that day when the dreaded words were spoken to me, "You have breast cancer." I was very blessed that Dr. Carr was able to take care of me because I knew his reputation for helping many breast cancer patients. When I saw him after my diagnosis, he was very reassuring, as the cancer was caught very early, and we spent considerable time discussing treatment options. He felt I would be a good candidate to participate in the Lumisight trial.

I want to tell you the most important parts of my life are my family. Being a wife, a mother, a nana to five, a sister, aunt, and friend are the roles that I truly value. I wasn't ready to let go of either of those roles. I was only 61 years old when I was diagnosed. The next chapter of my life was just beginning. My husband and I love

traveling together, especially on cruises and spending time with our grandchildren. I wanted to see the world with my husband and see my grandchildren grow and create their own lives. I wanted to experience all the birthdays, graduations, and weddings. So after speaking with Dr. Carr and my husband, I decided to participate in the trial.

I am very grateful that I was chosen for the trial, as Dr. Carr found additional cancer cells during my first surgery that might have been missed if not for the Lumisight. Dr. Carr was able to excise those additional cancer cells, and following my recovery, I received radiation treatments. I was put on medication for five years and have just graduated to less frequent mammograms, which have found no evidence of reoccurrence.

I feel like Lumisight may have saved my life. Since my surgery, I've vacationed in Alaska, which was on my bucket list. I've been able to attend high school graduation and a college graduation of my grandchildren. Please remember my

story as you consider your decision today. You can make the difference in someone's life and allow them more time with their loved ones. Thank you for your time.

DR. ROYAL: Thank you.

Speaker number 6, please unmute and turn on your webcam. Will speaker number 6 begin and introduce yourself? Please state your name and any organization you're representing for the record. You have 5 minutes.

DR. WILLEY: Good afternoon. My name is Shawna Willey. I'm the Peterson Chair of Breast Cancer Research at the Inova Schar Cancer Institute in Fairfax, Virginia. I'm a surgeon and have spent the vast majority of my 36 years in practice treating breast cancer patients and advancing surgical technology for the benefit of breast cancer patients. I am a former president and former chairman of the Board of the American Society of Breast Surgeons and also a member of the Data Safety Monitoring Board for the Lumicell trial.

Breast cancer is an emotional disease; you've heard that. The day a woman is told she has breast cancer is a day that is indelibly etched in her memory and a day that alters the course of her life forever. In fact, it makes such an impression, that I've had patients tell me decades later the exact words I used when I told them of their diagnosis and how those words made them feel.

In the course of my career, I have constantly strived to make things better for breast cancer patients. I have embraced new technology that held promise for making the experience of dealing with breast cancer a little better and a little easier. For instance, one of the things that I helped to popularize and have written extensively about is the procedure of nipple-sparing mastectomy. For a woman who needs a mastectomy, preservation of all the skin of the breast, including the nipple, and even newer techniques to preserve sensation, help to preserve a woman's body image and improve her quality of life.

I have participated in clinical trials for technologies that would improve survival; decrease the extent of surgery; enhance the cosmetic outcome; decrease the sequela of cancer therapy; or shorten the length of therapy. All of these things matter to women. They want what will give them the best long-term survival with the fewest side effects.

But let's talk about margins. Positive margins are the bane of a surgeon's existence. We would all like to say that we never have to reoperate for margins; however, the reality is, as you heard this morning, that since we don't have microscopic vision, we cannot clear the margins with the frequency we would like. Taking out all the cancer is the most basic of effective surgical cancer therapy, and yet we fail up to 30 percent of the time.

Patients are counseled that if the margins are not clear, they will need to return to the OR for another operation. Many times when a woman hears that she might need another operation to

clear the margins, or after surgery when she is told she has a positive margin, she decides to have a mastectomy because of the belief that a mastectomy will be better. Studies show, however, that mastectomies are not guarantees of disease-free survival, have no better survival than a lumpectomy, and in some cases are even worse.

I was invited to serve on the DSMB for Lumicell in 2017. I was not at a participating site, although after I read about the technology, I would have liked to be an investigator. My role rather was to review the protocol prior to enrollment and routinely evaluate the progress of the study with specific attention to safety, study content, and integrity of the data.

The DSMB gathered data, and had extensive conversations, and made recommendations regarding the reported reactions that might have been due to Lumisight. During the course of the review of these adverse events, the DSMB did not feel the need to stop the study. I believe that the benefits of Lumisight outweigh the risks, given

that the serious adverse events were few and managed immediately, leaving all patients able to move on to get their lumpectomy, and without permanent harm.

There have been many devices to address the problem of positive margins, but none like Lumicell. Lumicell interrogates the lumpectomy cavity, making the readings an immediate indicator of whether cancer was left behind, and if so, where it is. The trial data show that there were trial participants who benefited from the Lumicell procedure, as you've heard today.

The ultimate test of a new technology is improvement in survival. We don't have that data with Lumicell yet; however, we can demonstrate improved outcome by a decrease in the number of women requiring reoperation for excision, thereby improving cosmesis, decreasing time to adjuvant therapy and decreasing cost for the healthcare system and the individual. Most importantly, though, we are improving things for the woman who has breast cancer. There is nothing that brings a

smile more readily to a woman's face during her postoperative appointment than the words, "Your margins are clear." I believe that the Lumicell system will allow more women to hear those words, and I look forward to being able to use it myself. Thank you for your time.

DR. ROYAL: Thank you.

Speaker number 7, please unmute and turn on your webcam. Will speaker number 7 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have 5 minutes.

DR. CLARK: Hi. Thank you for letting me participate today. My name is Dr. Patricia Clark, and I am a breast surgeon in Scottsdale, Arizona. I participated in the Lumicell trial. I have no financial disclosures and I want to give you some of my perspectives on challenges we face continuing to make improvements in surgical outcomes for our breast cancer patients.

Survival rates, as were just mentioned, actually improve with breast conservation and

radiation than with mastectomy, and our goal is to preserve the breast and avoid unnecessary mastectomies. A key component of my surgical practice is oncoplastic surgery. This is a surgical approach that combines principles of plastic surgery with principles of cancer removal surgery to avoid the cosmetic deformities that often occur as a result of traditional lumpectomy procedures.

I'm passionate about helping patients in many ways and helping them preserve their presurgical breast appearance to the extent possible that makes a big impact on their mental health. I've also been heavily involved working with major surgical societies to share this knowledge.

Some of the considerations that we think about with oncoplastic lumpectomy are these techniques enable us to perform lumpectomies on patients who may have it arise to need a mastectomy, secondary large tumor size, or unfavorable locations. Oncoplastic procedures are

more complex than simple mastectomies, however, and they often require a surgical team pairing a breast surgeon to do the oncologic component with a plastic surgeon who reconstructs the defects. The reconstructions can involve extensive rearrangements of the remaining tissues in the breast to fill the defects and reshape the breast to restore normal appearances.

Since the original lumpectomy cavity is obliterated when we apply oncoplastic techniques, which involve moving tissue from the original locations and orientations, re-excisions for positive margins can be quite complicated. If a pathology report shows a positive margin, that can lead to a mastectomy. Pathology reports often become available, at the earliest, 3 to 5 days post-op, but it can be up to weeks in some systems. Re-excisions are feasible if they're performed very early, prior to the tissues healing in solidly, but there are multiple barriers to restrict our ability to get that patient back into the OR in a timely manner. The OR availability can be very restricted

in many hospital systems.

Because these tissues have been rearranged, we have to coordinate the surgical schedules of both a busy plastic surgeon and a breast surgeon, who are already fully booked. The plastic surgeon is needed at that second case because only that plastic surgeon knows how to dismantle those rearranged tissues to identify the original lumpectomy bed that had the positive margins. Of course, even then, there's no certainty that we'll ever find the original tissue, even with multiple surgeons in the OR, so sometimes mastectomies are unavoidable if we have to go back. For patients who have undergone standard lumpectomies, it's this timeliness, and these challenges are the same as we've already heard. Some surgeons are even taking additional shave margins at the time of the additional surgery to reduce the rate, but that's resulting in unnecessary removal of more tissue.

For patients, there's an emotional devastation involved in the return to the OR for re-excisions, but there's a financial cost as well.

In a study conducted by UT Health and just published in Annals of Surgical Oncology last month, they looked at over 17,000 breast cancer patients undergoing breast conservation who needed re-excision, and that was noted to increase cost 24 percent. In commercial carriers, that re-operation added $21,607 to their cost of care, and that was $8,559 for the Medicare patients. There's also a 54 percent increased risk of complications in the commercial cohort and 89 percent in the Medicare cohort.

A lot of those re-excisions are ductal carcinoma in situ, and in those, the tumor cells are confined in the milk ducts, so we can't see or feel them during surgery. In my personal experience, patients strongly wish to participate for reassurance that I got it all, and I recall one patient that I had who preoperatively looked like it was a very easy excision, a well-defined tumor. I didn't foresee any problems. I took the tumor out, and the final pathology showed that I had negative margins; however, the Lumicell study

showed that there was residual disease. I took an additional shaved margin, where I was guided, and there was DCIS in that shave that I would have never known about, and I would have assumed that she was negative.

So I think it's our responsibility of our patients and the healthcare system to ensure our first operative encounter definitively eliminates the cancer and restores the form and function for our patients, and this type of technology I think is necessary to do so. Thank you.

DR. ROYAL: Thank you.

Speaker number 8, please unmute and turn on your webcam. Will speaker number 8 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have 5 minutes.

DR. DIAZ: My name is Dr. Roberto Diaz. I have served as a consultant to Lumicell, but I am here today to share my perspectives as a board certified radiation oncologist with a career spanning since 2009. I am currently serving as a

breast radiation oncologist at the H. Lee Moffitt Cancer Center in Tampa, Florida, and I have done so for almost 10 years, and concurrently work for over six and a half years at Morton Plant Hospital in Clearwater, Florida.

Post-lumpectomy radiation decisions encompass a spectrum of approaches, ranging from whole breast radiation with or without a boost, to accelerated partial breast irradiation, or even the strategic omission of radiation. Final pathology plays a pivotal role in directing radiation oncology decisions, with surgical margin status being a crucial determinant. For invasive breast cancer, surgeons often opt for re-excision in cases of positive margins; while close, less than 2-millimeter margins may necessitate whole breast irradiation with a boost. However, margins of 2 millimeters or more can allow for a streamlined approach with whole breast irradiation alone.

Intensifying radiotherapy with a boost, while effective, comes at the cost of prolonged treatment duration and increased side effects,

including acute symptoms such as breast pain and skin reactions, dermatitis, and long-term effects such as breast fibrosis and telangiectasia, spider veins. The Lumicell technology emerges as a potential game changer, presenting the prospect of achieving negative margins and wider negative margins post-lumpectomy. This holds promise in de-escalating treatment, a critical consideration in the era of personalized medicine.

Accelerated partial breast irradiation offers the benefit of equivalent efficacy as whole breast radiation in select cases, with the additional advantage of treating a smaller volume of breast tissue, resulting in fewer toxicities. The integration of the new Lumicell technology is particularly crucial in this context, as it not only enhances the precision of margin assessment, but also provides the potential for achieving wider negative margins post-lumpectomy. This technological advancement aligns seamlessly with the pursuit of personalized medicine, optimizing treatment outcomes for breast cancer patients.

According to the new 2023 guidelines from the American Society of Radiation Oncology, ASTRO, for accelerated partial breast irradiation, if the surgical margin is less than 2 millimeters, the recommended volume of breast tissue receiving this high dose of radiation should be larger. Conversely, if the surgical margin is 2 millimeters or greater, the current guidelines suggest treating a significantly smaller volume of the breast. The ultimate de-escalation is the omission of radiation altogether.

Several published and ongoing studies incorporate diverse clinical, histopathological, and genomic factors to identify patients eligible to safely avoid post-lumpectomy radiation. Notably, in many of these trials, patients are ineligible to forgo radiotherapy if margins are less than 1 millimeter. Lumicell technology's role becomes crucial in this context, offering enhanced precision in margin assessment.

Studies have shown that post-lumpectomy radiation for positive margins results in

approximately double the recurrences compared to treatment for negative margins. The Lumicell technology introduces a significant advantage by identifying previously unknown residual disease in patients, as indicated by their 2023 New England Journal of Medicine manuscript, of about 7 and a half percent. This data not only highlights the technology's efficacy in enhancing margin assessment precision, but also underscores its potential as a transformative force in breast cancer care.

Lumicell technology stands as a beacon of progress, addressing historical challenges in obtaining negative margins and significantly reducing the need for re-excision surgeries. This translates to streamlined surgical processes, diminished physical and emotional burdensome patients, and an accelerated treatment timeline. Such advancements not only align with the principles of patient-centric care, but also contribute to a more positive and personalized experience for those undergoing breast cancer

treatment.

In conclusion, I believe that Lumicell's technology ability to clear surgical margins and provide wider negative margins holds great potential for de-escalation strategies. With the status of margins influencing critical treatment decision, this technology emerges as a valuable ally, guiding us towards a more refined and tailored approach in breast cancer care. I appreciate your attention to these considerations and remain open to any inquiries or discussions on this transformative technological advancement. Thank you for your time and consideration today.

DR. ROYAL: Thank you.

Speaker number 9, please unmute and turn on your webcam. Will speaker number 9 begin and introduce yourself? Please state your name and any organization you're representing for the record. You have 5 minutes.

DR. MONTES: Good afternoon. My name is Dr. Jennifer Montes. I'm a general surgeon by training, specializing in diseases of the breast.

I completed my undergraduate training at Cornell University. I hold a master's degree in public health from Columbia University. I attended medical school at Temple, followed by residency training at Lenox Hill in New York and a breast fellowship at NYU. During that time, I also completed breast cancer externships at Memorial Sloan Kettering, St. Luke's Roosevelt, and Columbia University. Most of my practice is in the surgical treatment of breast cancer. I currently practice in Hunterdon Medical Center in Flemington, New Jersey.

I've served as a consultant for Lumicell in the past, but today I am speaking on behalf of my patients, myself, and the patient advocacy organization called Evolve Pink. After witnessing the far too common struggles women experience while dealing with breast cancer, I personally wanted to do more, so in addition to my medical practice, I became the founder and medical director of Evolve Pink, a nonprofit organization.

Our mission at Evolve Pink is to give women

the tools to transform the most catastrophic event in their lives into the catalyst for empowerment, self love, and greatness. Evolve Pink is a highly network, comprehensive women's cancer support organization, providing nonclinical, individualized care and support to women affected by breast cancer.

As a clinician, I always thought that the best moments would be when I told my patients that they are cancer free and that they can return in six months, though I quickly realized that our medical community doesn't have enough to offer patients that would allow her to close this chapter in her life so easily.

Women ending their treatments are faced with new fears about recurrence while also losing the constant support and guidance of their healthcare system, and this is the space that Evolve Pink steps in to fill. Examples of our services: our information sessions; education regarding important questions to ask their doctors; meditation; journaling; healing; arts classes; group exercise;

and a multitude of holistic modalities, including massage, Reiki, and yoga, as well as many simple social events for our survivors for them to form a community.

For women choosing to undergo breast conservation surgery, one of the largest sources of anxiety is the concept of needing clear margins, as we have discussed. Prior to undergoing lumpectomy, it is clearly explained that in order to be a successful surgery, all sides of the area removed must be free of cancer cells.

I explain to patients that as far as I can see, feel, touch, x-ray, ultrasound, I am never leaving the operating room thinking I am leaving cancer behind; however, I simply do not have microscopic eyes yet. They often laugh at this. This means the patient is waiting close to a week before they have concrete answers regarding their marginal status, and even at this point, pathology is not always accurate. Patients wait and hope that they will not have to return to the operating room due to cancer missed during this surgery.

I'm sure you can imagine that this time brings great anxiety and suspense for my patients. This is the space where Lumicell can help, a true real-time surveillance of the exact site where the tumor was removed, because let's face it, if we need to go back for a second time, even if we try the best that we can, we may not be in the exact location where those residual cancer cells resided. It can be missed, or perhaps the pathology was inaccurate in the first place and missed cancer cells that were left behind not on the margin. The best of science is just not that perfect yet.

I could give many accounts of patients that have been negatively impacted by having to return to the operating room for positive margins, but one example that stands out in my mind was a young 38-year-old patient early in my career. She was diagnosed with DCIS. She underwent all the appropriate preoperative workup, including an MRI which showed a small area of disease.

She underwent what was seemingly a simple lumpectomy. All six margins returned with positive

breast cancer cells. Given her prior surgical workup, this was quite a surprise to us. We returned to the operating room for a second time. The margins were largely excised and, again, I was sure that we had clear margins. Her pathology returned with frank, abnormal cells on all of the excised margins. Again, this was a great surprise considering that this was not seen on mammogram, ultrasound, or MRI.

This news was devastating for the patient, as you can imagine, and she opted finally for having a bilateral mastectomy with reconstruction, which she did not want. Although this procedure usually goes very straightforwardly and without complication, this patient had a very difficult time postoperatively. She was later diagnosed with both anxiety and depression. A year and a half after what appeared to be a seamless reconstruction, she had her implants removed due to her belief that the implants were causing her a multitude of unwanted symptoms. She quit her job of over 20 years as a paramedic, which she loved.

I've remained in close contact with both she and her wife, and this has impacted every aspect of their lives, including their marriage.

When I first saw Lumisight demonstrated, I immediately thought of this patient and wondered if her course could have been changed had this technology been part of my armamentarium at the time of her surgery. As a breast cancer surgeon, I cannot think of a single more helpful tool, not only for surgeons, but also to instill additional confidence such that we have removed as much as we can in real time.

I believe that nothing is perfect, but incremental improvement that gets us one step closer to eliminating the possibility of telling a patient they require yet another visit to the operating room pushes us in the right direction; and more importantly, having a product that can ease the fear of unknowingly leaving breast cancer behind that otherwise are not assessed by pathology. This would be a complete game changer for us who work in this field. Thank you all for

your time and consideration.

DR. ROYAL: Thank you.

Speaker number 10, please unmute and turn on your webcam. Will speaker number 10 begin and introduce yourself? Please state your name and any organization you're representing for the record. You have 5 minutes.

DR. WAPNIR: My name is Irene Wapnir, and I have no financial relationships with Lumicell. I am a breast surgeon and professor of surgery at Stanford University School of Medicine, as well as Director of Breast Cancer Surgical Clinical Research at the Stanford Cancer Institute. I have over 35 years experience in the field of breast surgery and clinical trials, including studies using fluorescent agents intraoperatively. With respect to today's presentation, I was co-investigator and institutional PI for the Lumicell DVS studies.

Every day, surgeons and patients face the uncertainty of lumpectomy margins and the challenge of achieving tumor-free margins according to

recommended guidelines. For over 35 years, since lumpectomy became an accepted option in the treatment of breast cancer, the issue of what constitutes a negative lumpectomy margin has been analyzed and debated. We're all dependent on the microscopic evaluation performed by pathologists, where a representative sample of the surface of the removed cancer is examined and a determination is made as to whether the resection has completely removed all the tumor.

It is a labor-intensive process for pathologists, but at the same time, a limited methodology. Specifically, a 5-micron section is taken from an approximately 4-millimeter thickness block of tissue, and it is examined under the microscope. It is from this limited sampling that a margin is declared involved or clear. At best, this is a representative sample, and therefore likely misses some involved margins and does not direct the surgeon to re-operate to remove tumor left behind in the lumpectomy cavity.

Lumicell DVS is a smart and novel technology

focused on detecting residual tumor in the lumpectomy cavity. Interrogation of the lumpectomy cavity is a superior approach to that of evaluating the surface of the removed tissue, as has been done up to now by pathologists and other margin-directed technologies. It is easier to administer the fluorescent optical agent, and equally easy for the surgeon to insert the device in the lumpectomy cavity and scan it.

I have done approximately 65 of these procedures myself and can attest to that. I have been surprised to see that this imaging system can detect small volumes of residual disease, a benefit, in my opinion, of the pegulicianine agent that is enzymatically digested by both tumor cells and tumor-associated macrophages. As such, it is probably detecting a micro environment around the tumor that harbors tumor cells or precursor cells that could transform into tumor cells that defy easy detection. Thus, this methodology will not only reduce the number of re-operations that are a result of positive margins, but may decrease the

number of local recurrences to unprecedented low numbers.

As a technology, pFGS-guided surgery provides a more rational approach that can complement and add to the current laborious and imperfect evaluation of margins. I believe our group's research has effectively shown that scanning the cavity for fluorescence can reduce the number of re-operations for positive margins. In closing, I will note that while no technology is perfect, Lumicell DVS has shown that it can improve the accuracy and ultimate long-term success of breast-conserving surgery. Thank you for your time.

Clarifying Questions (continued)

DR. ROYAL: Thank you very much.

In the next few minutes, we're going to give Lumicell the opportunity to answer a question that Dr. Greenberger posed earlier. Maybe they could repeat the question and give us their answer.

DR. FERRER: Thank you for the opportunity. Dr. Greenberger had a question about a patient with

acute respiratory failure unrelated to Lumisight. Dr. Shelley Hwang is going to go over the narrative of that patient.

DR. HWANG: So this is my patient, who is a 69-year-old white female who is diagnosed with invasive ductal cancer of the left breast. In January of 2021, she was enrolled in the Lumisight study and was injected with Lumisight, and had an uncomplicated surgery. After surgery, her vital signs were stable in the post-op area, but shortly thereafter the patient was found to be unresponsive and had minimal respiratory effort. This required intubation. The patient became hypotensive, and she was transferred and admitted to the intensive care unit. She was briefly placed on pressors.

The patient developed atrial fibrillation with rapid ventricular response during her ICU stay, and with a cardiology consultation, she was found to have had a mild myocardial infarction. She had initially been intubated but was able to recover shortly thereafter, and was extubated within the first 24 hours. She had a cardiac

catheterization, which showed minimal coronary artery disease and normal ejection fraction. She recovered very quickly from all of this and was transferred back to our service for further management, and a month later, she was able to come for her follow-up appointments.

The assessment was that this patient suffered acute respiratory failure and somnolence, and this was found to be a grade 4 event and not thought to be related to the study drug or advice. I'd be happy to answer any additional questions Dr. Greenberg may have.

DR. GREENBERGER: Thank you for those details. Just to clarify, does this account for the notation in the records where it said "acute myocardial infarction and hypotension?" Is this the same patient or is this a different patient?

DR. HWANG: Yes, it is. Yes, they were both sustained by the same patient.

DR. GREENBERGER: Okay. Thank you, and I appreciate your explicit details.

DR. HWANG: Thank you. And if I could, I'd

like to have the opportunity to just provide one additional point of clarification regarding some of the questions regarding patient-level versus image- or tissue-level sequelae of either a true positive or a false positive.

I just wanted to underscore that the only time that patients underwent a second operation during this study was if the final pathology showed that the final margin was positive. In no instances with the images themselves, whether they were true positive or false positive, were they ever an indication for the patient to have a second surgery; therefore, the immediate sequelae of a patient having a falsely positive image was that the patient would undergo re-excision of that margin intraoperatively. And I just wanted to make sure that everyone was clear that the images themselves never prompted or necessitated a second operation.

I'd be happy to answer any questions if you have any.

DR. ROYAL: Thank you for that

clarification.

The open public hearing portion of this meeting is now concluded.

DR. SKATES: Sorry. I did raise my hand to ask a question.

DR. ROYAL: Okay. Dr. Skates?

DR. SKATES: I want to thank Dr. Shelley Hwang for her clarification about the decision process with the images in the study.

My question had been having the patient-level sensitivity and specificity, and positive predicted value, quantification, and metrics like that be the primary metric by which to judge Lumicell rather than the image-based or excision-based, which can be multiple for each patient, because the decision is at a patient level whether to undergo Lumicell or not; it's not at a more granular level than that. So when you mentioned this patient level versus image level, I thought you were going to make some judgment about which level of metric you were going to support or find to be primary.

Did I miss something there or misjudge something, misunderstand?

DR. HWANG: No, I just wanted to provide clarification that patients did not undergo a second surgery on the basis of a falsely positive Lumicell signal. I don't think that was clear in some of the back and forth that happened with the first discussion.

With respect to the question you just answered, I'm not sure that I am in a position to answer it, but I think the FDA did address this question, and I think I'll probably just leave it at that, but thank you very much.

DR. SKATES: Okay. But there was a saving of second-look surgery based on the images, right? So there were 9 patients that benefited from this in the study from avoiding a second operation, which I think is a great positive. I think that sort of seals the deal, but there are costs to that, and I'm trying to bring out the positives there, but also understand the balance of negatives from a surgeon's judgment about that, and it's been

hard to get that. Everything's been positive about this. Most of the presentations have been about the positive aspects, but I'd like to get a sense from you about the balance of the positives and the negatives. Thank you.

DR. HWANG: Yes. So very briefly, I think the clear positive is if the patient were able to avoid a second operation. The clear downside is that if the signal is falsely positive, they would have re-excision of an additional area of tissue, which may not contain cancer. That would happen only at the time of the first operation and would never result in a second operation unless that margin remained positive despite the re-excision.

So I think the balance is whether avoiding a second surgery, or an attempt to avoid a second surgery, is worth having to re-excise a potentially negative margin. I think you bring up some excellent points, and I think it's really going to be up to the panel and the FDA to determine whether that trade-off is beneficial.

DR. SKATES: Right. Thank you very much.

DR. ROYAL: We will now proceed with the charge to the committee from Dr. Alex Hofling.

Charge to the Committee - Alex Hofling

DR. HOFLING: Okay. Now for the charge to the committee, I'll run through the discussion points and questions for the committee, and then turn it back to Dr. Royal.

The first point for discussion is to discuss whether the observed performance of Lumisight for patient-level detection of residual cancer, tissue-level sensitivity, and tissue-level specificity provide sufficient evidence of effectiveness. The next point for discussion is to discuss the risk of serious hypersensitivity reactions associated with Lumisight and the adequacy of risk mitigation and assessment strategies under consideration.

Then our voting question, do the benefits of Lumisight outweigh its risks? If yes, describe the clinically meaningful benefit and the risk mitigation measures that are recommended. If no, provide recommendations for additional data and/or

analyses that may support a positive benefit-risk assessment of Lumisight.

I'll turn it back to you, Dr. Royal.

Questions to the Committee and Discussion

DR. ROYAL: The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning its wording.

We will proceed to our first question, which is a discussion question. Discuss whether the observed performance of Lumisight for a patient-level detection of residual cancer, tissue-level sensitivity, and tissue-level specificity provide sufficient evidence of

effectiveness.

DR. SEO: Dr. Royal, this is Jessica. Before we begin the discussion, just a friendly housekeeping reminder to all participants, please remember to turn on your video when speaking and to state your name before your comments. Thank you.

DR. ROYAL: Dr. Griffin?

DR. GRIFFIN: Yes. Marie Griffin, Vanderbilt University. It's hard to say about sufficient, but I just want to say, the 62 patients that had positive margins, only 8 or 10 were identified by the Lumisight and 8 or 9 were prevented from having excision. But again, more patients were also identified with cancer that had negative margins, and this caused some additional surgeries, 2 or 4, and also additional worry on the patient's part.

So I think initially I was very excited that this would significantly decrease re-excisions. It did, but not as much as I had hoped, and I think the idea of alleviating the worry of negative margins and additional tumor has been

overemphasized because we now picked up more cancers. And as we know, a lot of these cancers will be taken care of by radiation. We don't know which ones.

So I don't think it's as quite as beneficial as maybe I was led to believe initially. So I'm still on the fence about sufficient evidence of effectiveness, but definitely there is some efficacy. I think the big concern is that we're really using surrogate endpoints, so we don't really know how this will ultimately affect patients' outcomes. Yes, I think that's all I had to say.

DR. ROYAL: Okay. Dr. Pearson?

MS. PEARSON: Thanks. In my many years of being a speaker during the open public discussion, I saw how often sponsors were legitimately frustrated when members of the committee would say, "Oh gosh, if only this study had been designed differently," because the study's been done, and the design and the endpoints at least were agreed upon with the agency, and in this case, the agency

has been very clear that they agreed upon these endpoints.

But I'll just point out that the performance of this system for patient-level detection and removal of residual cancer is as -- the agency says it's a surrogate endpoint, but I think it's far from proven to have a relationship -- it's certainly not a one-to-one relationship with the bad outcome that we hope it's a surrogate for. The bad outcome of a local recurrence, which then has an increased risk of death, is in the range of 5 percent. So if the 3 percent that the agency had set as a lower bound for patient-level detection of residual cancer was a one-to-one relationship, well, that would be great; but it's not, and we don't know what it is.

So it's really a dilemma to know what's sufficient in this case. 2.5 percent of patients avoiding a second surgery that they would have had otherwise, in some women's mind, if they have fantastic informed decision making, with explicit, absolute reduction of risk, not relative reduction

of risk, some -- maybe a lot -- women would happily consent to a procedure that lowered their risk of a second surgery by 2.5 percent, but that's a tough co-primary endpoint. That's what I have to add to the discussion. That's all for me.

DR. ROYAL: Thank you.

Dr. Burstein?

DR. BURSTEIN: Hi. Hal Burstein. My concern here is also about the endpoint because detecting every shred of cancer is not the goal of breast cancer management anymore, and it's largely because of our outstanding American surgeons who have led the world in doing less surgery. For instance, would FDA approve an axillary lymph node dissection in a patient because of positive sense of the lymph node at this point? Because we know that 20-25 percent of those patients will have residual disease in the axilla. In a more contemporary example than Z0011, the recent SOUND trial showed that if the ultrasound is negative, you can avoid a sentinel node biopsy even though 14 percent of those patients had cancer in a sentinel

lymph node, and in these instances, we're talking about invasive cancer, not DCIS at the margins.

Now, nobody wants re-operations, nobody wants local recurrence, but I think the idea that the endpoint that matters is detecting cancer isn't really the one that either the patient advocates or community members who just spoke so articulately were looking for. They're talking about things like tailoring radiation treatment or avoiding re-operations or reassurance, but that's not the data we have. And I think there may have been a miscall here on what the real endpoint should be, and that's what worries me about this, still.

DR. ROYAL: Thank you.

Dr. Vasan?

DR. VASAN: Hi. Neil Vasan. I just wanted to also put out that I wonder if there could even be a reframing of the question in the sense that there were three primary endpoints, three co-primary endpoints, the detection of the residual cancer, which I think the prior speakers, I agree with everything that's been said. I think there's

a beauty in the eye of the beholder question there; is that really the right endpoint? But that percent was met.

The tissue-level sensitivity, which was not met, that lower bound was the 36 percent, which was less than 40 percent and then the tissue-level specificity which was met. And the FDA provided language that, depending on the clinical context, a lower sensitivity below 50 percent might be balanced by a higher value of the other metric.

So it seems like a reframing of this discussion point would really be, based on the FDA statutory language, is that balanced by the higher value of the other metric, i.e., the specificity? And we certainly have the Youden index, and we have the ROC curve data that, I think, show that there is an improvement qualitatively and quantitatively, but I think that's another reframing of this question; is that higher value of the other metric outweighs the fact that the sensitivity metric was not met.

DR. ROYAL: Dr. Skates?

DR. SKATES: Thank you. My concern here is setting a precedent of using tissue-level sensitivity and tissue-level specificity for what I regard as a secondary endpoint, with the primary endpoints being patient-level sensitivity and specificity. The FDA did provide that as a secondary endpoint, even though it wasn't prespecified, and those secondary endpoints, even though they didn't meet the cutoff of the tissue-level endpoints, they're enough to convince me that on balance, we've got a positive study here. As this discussion question is framed, though, I would have to answer a no because I do not find tissue-level sensitivity and specificity, or tissue-level metrics, to provide sufficient evidence for patient effectiveness at the patient level.

So a positive and a negative there; one, I'm concerned about setting a precedent with this question saying that tissue-level metrics are sufficient, and second, the positive is that the secondary analysis that FDA did provide would

result in an affirmative answer from me to this question. Thank you.

DR. ROYAL: Okay.

Dr. Richardson?

DR. RICHARDSON: Hello. Dr. Richardson, pathologist from Johns Hopkins. I guess in coming down to it and listening to the patients and the surgeons in the public forum, the most important thing to patients and surgeons, it seems, is avoiding second surgery. And when I look at the numbers on slide number 38 of the Lumicell presentation, there were 62 patients with positive margins after the standard of care lumpectomy, and of those 62, only 15 percent could avoid second surgery.

So the vast majority still had to go on to second surgery, and I guess that's something, but it's certainly not a slam-dunk wonderful result, in my opinion. Is it worth the risk? I think probably it is worth the risk, but it may be something that needs to be made clear to patients who are signing up for this, that it only slightly

reduces your risk of having a second surgery from what standard of care would do if you have positive margins.

That being said, in my opinion, the false negatives are the biggest issue. The false positives -- to reiterate what Shelley Hwang said, the problem with a false positive image is you have to take a few extra shave margins during the procedure. Well, they're already taking unnecessary shave margins during the procedure blindly. I mean, that's standard of care now, is to blindly take these additional shaves. So I don't really see a risk to the false positives. It's really the high level of false negatives that I see as the downside to this. Thank you. That's all.

DR. ROYAL: Dr. Leitch?

DR. LEITCH: Breast cancer advances have always been kind of incremental. When you have a clinical trial, it may have a 2 or 3, or 4 percent benefit over the last thing that was done. So this kind of falls in that category, that it's not a

home run in the sense of really making a major difference because as was pointed out, still a fair percentage of people had to get a second surgery who had positive margins, and I do think it is important for patients to have a realistic expectation of what the benefits are.

I think Dr. Burstein was saying how we're trying to do much less with surgery, but I'll tell you, in practice, if you have a positive margin, everybody's telling you to go back. I mean, you don't get to get by with a positive margin, typically. It's hard to convince radiation oncology to radiate somebody with a positive margin. And then we have the issue of the desire to avoid radiation, and yet there are people, as in this study, where their partial mastectomy margins were clear, but then the Lumicell margins were positive. So for a patient trying to avoid radiation, you would like to have pretty good certainty that the margins are clear.

So I think this technology potentially has selected use, although it wasn't really addressed

in this trial, in special circumstances like ductal carcinoma in situ, invasive lobular cancer, large areas of enhancement on MRI; or in the circumstance as was mentioned, trying to do oncoplastic surgery where you're going to rearrange that cavity margin, and to have to re-excise at a later time is not very reliable, at best. But I think the FDA is saying that this study met the prespecified endpoints for the patient-level endpoint, which was the detection of cancer, and that they accept, for imaging purposes, this tissue-level endpoint. So I'm not sure we can hold Lumicell to a higher standard than other devices might experience for imaging.

I also thought it would be better. I thought that there would be a higher success rate in terms of identifying during surgery so that you wouldn't have to re-excise, and I think there's the chance that that can improve. It sounded like they thought they had trained the surgeons pretty well in the technique, but I think any technique, the more you do it, the better you get at it, the

better the interpretation is, and people have to be trained and do it properly so that it has a chance to be beneficial for the given patient. Thank you.

DR. ROYAL: Dr. Xiong?

DR. XIONG: Chengjie Xiong from Washington University. First of all, I would like to just start by saying the trial is targeting a really important medical question. With that said, I think my second comment is, although none of us want more cancer patients or a second surgery, the trial presents the efficacy from a very small number of events. We're talking about a single digit number of patients who are benefited in terms of avoiding second surgery, and the other endpoint like sensitivity, we're also talking about a small number of people or tissues.

So from a statistical point of view, when you are dealing with those numbers, a smaller number of events, it's really, really hard to be convincing in terms of whether this is a real signal. I think that's my primary concern. We simply need more data, although everybody, every

single patient, is important. Anything helping a single patient is precious, but from a statistical point of view if you want to say efficacy, we need a bigger number of patients and we need more convincing statistics based on that bigger sample size. That's my comment.

DR. ROYAL: Dr. Rosenthal?

DR. ROSENTHAL: Yes. Thank you. So it seems that it's very hard to go back and doubt the prespecified endpoints, which were largely met. I think that's really important in that it may be a small number, but it is a small number that met those prespecified endpoints, and that was the goal of the study, and it met that. And I very strongly agree that incremental gain is very important in this kind of disease, and as the technology gets implemented and surgeons interact with it, typically, things get better.

I do understand the nuances of the tissue-level data and not setting a precedent, and I think that's a very valid point. On the other hand, breast cancer is very unique in the sense

that you don't have frozen sections, and almost most cancer types, you can send for frozen sections, and that's kind of your tissue-level assessment, and surgeons don't have that in breast cancer because the fat doesn't amend itself to that.

So to have a tissue-level assessment in breast cancer is a unique opportunity for surgeons, and from a surgical perspective, being in the cavity at the time and having that tissue-level specificity is very helpful from a surgical perspective; in other words that feedback immediately about the extent, even if it's a guess, just like frozen can be reversed. I think this is really important.

So I think they met the endpoints that were relevant, incremental gain is critical, and the tissue level is important to the surgeon at the time of surgery, which cannot be substituted for a frozen section, which is what we would typically do in that setting. Thank you.

DR. ROYAL: Dr. Fisher? Ms. Fisher?

MS. FISHER: Yes. Here I am. Sorry. From the patient advocacy side of things, having worked with a lot of different patients at different stages, and myself being an invasive cancer patient, certainly you don't want to have second surgeries, third surgeries -- that's a big part of what you don't want -- but what a cancer patient definitely wants is they want someone to tell them you have clean margins as best that they can, to their ability. A lot of this is comes down to art and not science along the way, as much as we've progressed along the years.

I agree with both Dr. Leitch and Dr. Rosenthal, this isn't a home run, this isn't something that's magical, it's not the panacea that we all would love to see, but it is maybe one more arrow in the quiver that is an option. I think it was a well-run study and they did everything they needed to do. So I think that it is something that is worth having out there for the ability and an option. That's my feeling on it from my perspective. Thank you.

DR. ROYAL: Dr. Bryant?

DR. BRYANT: Yes. I've done a few of these, and it just reminds me how important is what we all do, so one kudos to the agency for their diligence and engagement and also to the company for conducting the study. And I'll just echo -- when I raised my hand, I didn't realize that Dr. Richardson, Dr. Leitch, and Dr. Rosenthal were going to hit on key points. I won't go into the data points, but when we think about the prespecified endpoints and how the company performed, I agree that there are no perfect data sets, but innovation is tricky that way. Incremental benefit means something. And I'm not disagreeing with anyone of the panelists, but when we look at statistics, within those statistics are people, and I think we heard from those people, as well, and from some of the surgeons as well.

Ms. Fisher, I love what you just said around it's not magical. It's not magical in aggregate, but those patients that we heard from, they don't live in the aggregate, and it's multifactorial,

it's complicated, but each one of them, innovation like this I think adds value. What struck me was not just the impact on the patients, which is critical, but the impact of not just them, but those people who love them, the economic impact.

I heard about the fear, and of course this is not going to alleviate it for all, but if the answers to the following questions around risks and others, if there's a balance there, I think there's value here. And when we think about innovation, speaking from an industry point of view, first is safety, and I think everyone wants to be on the same side of safety as the agency. And when we think about promoting and protecting public health, that's what these companies do, that's what these surgeons do, and that's what you all do. So in order to continue to invest in innovation, to see that innovation get better and better, of course, it's a small set now, but as things evolve, I think there's more and more value.

So kudos to everyone of you for your diligence, how seriously you've taken this, but

what I would just say is if the answers to the rest of the questions provide balance, I would ask us to continue to think about those patients that it did benefit, those that they love and also those that love them. So I'll defer. That's the end of my response.

DR. ROYAL: Thank you.

Dr. Jacobs?

DR. JACOBS: I kind of agree with lots of other people. It's not a home run. It's certainly not the end answer that we would like to see, but it's a step, and it clearly benefited some patients. Did it benefit as many as we would like? No, but it met its endpoint. It did what they thought it would do.

Listening to Dr. Rosenthal, who is a surgeon, talking about two things, one is that the surgeons get better as they practice the technique, and it doesn't matter how good your training program is, you're still going to get better and practice the technique.

The second thing is that it's the first

step. We keep improving this. Are we there? No, we're not there, but should we reject something that helps even a small percentage of patients because it doesn't help the others? But it doesn't really harm them either. Those people who have to go on and have second surgeries have to go on and have second surgeries, and it won't change many of them, but it'll change a few. And to say because it doesn't change a lot of them, we're going to deny it to those that it changes seems wrong to me. That's kind of where I'm coming from.

DR. ROYAL: Thank you. I've been asked to summarize what I've heard, and I apologize if what I heard isn't the same as what you heard. But my impression certainly has been that there's general agreement that this trial met the prespecified endpoints, the endpoints that were specified by the FDA. I heard the word "home run" several times, and I think it's probably not very realistic to think that that's the way medicine advances, is by home runs. The word "incremental" was mentioned several times, and that's more commonly how

medicine advances, with small incremental steps.

I also heard that that we're hopeful that things will improve over time, that surgeons will get better at using this technique, and maybe the software algorithm could be improved. On the other hand, I think it is very important that patients have a very realistic expectation of what this new test will and will not do. I mean, we sort of have to rely on surgeons to be honest and transparent about what patients should expect. I also heard the word "magical," that this was not a magical advance, but I bet the patient who didn't have to have this second surgery would think it was pretty magical.

So those are my comments, and hopefully I summarized your comments.

Okay. We're going to take a quick 15-minute break, so we'll reconvene at 3:10 pm Eastern Time. There should be no chatting or discussion of meeting topics with other panel members during the break. Thank you.

(Whereupon, at 3:55 p.m., a recess was taken,

and meeting resumed at 4:10 p.m.)

DR. ROYAL: Welcome back. We will now move on to the next question, which is a discussion question. Discuss the risk of serious hypersensitivity reactions associated with Lumicell and the adequacy of risk mitigation and assessment strategies under consideration.

So the first thing we want to discuss is whether there are any questions about issues or questions regarding the wording of the question.

(No response.)

DR. ROYAL: There were no further questions or comments considering the wording of the question, so we'll open the question to discussion.

Dr. Leitch?

DR. LEITCH: I don't consider the risk from the hypersensitivity to be something that's overwhelming and should say that that's way more important than the benefits. I think certainly surgeons are used to experiencing allergic reactions to a number of things that patients receive while they're in the operating room, and as

has been noted, you basically have the support system around you to deal with those things and in most cases get the patient successfully through the intervention. And if it's anaphylaxis, of course, everything may have to stop and may have ICU care, but that's clearly a rare event.

So what has been reported here would not dissuade me from utilizing the technique. Like everything, when we consent patients, we talk to them about potential risks of reactions to medications, and that would be explained, and we would have our nursing staff who take care of the patients in the pre-op area be aware of what to watch for. So I don't think that the side effects that have been reported would prevent us from being willing to use the technology.

I think it would be great for the company to monitor these events, but I'm not sure in terms of some of the monitoring things of institutions that an institution might have to go through, that's already a certified institution by JCAHO in the operating room, I don't think they would require

other issues other than education of the staff and the physicians about the agent and the anesthesiologist so that everybody's aware that, like any medication, there can be a potential reaction, but not to put too much burden in terms of what an an institution would have to do to say they could use the agent. That's all of my comments.

DR. ROYAL: Thank you.

Dr. Pearson?

MS. PEARSON: Thank you. This is Cindy Pearson, the acting consumer representative. I think a postmarket study is reasonable, as the FDA has suggested. I would just also say that I would encourage the FDA to have preset continued participation requirements. Obviously, if the FDA is thinking of doing a study with a goal of a certain number of patients enrolled, that's one thing; but overall, with postmarket studies, there's often a a fall off in continuing in the trial. So I would encourage the FDA to establish some expected participation and expected quality,

to be honest, from the sponsor.

However, I don't think a REMS is necessary. They're very difficult for a sponsor to get out of, and I don't think, really, based on what all of the clinicians are saying, that the added benefit of an institution filling out paperwork to document that they understand that patients need to continue to be monitored after the initial IV and first few minutes of the IV infusion have gone past, I don't think there's all that much benefit for that, and that's all I have to say. Thank you.

DR. ROYAL: Okay.

Dr. Griffin?

DR. GRIFFIN: Yes. Marie Griffin, Vanderbilt. I guess in the next section we're going to talk about benefit-risk, but I just want to talk about numbers. I think we know that about 8 patients, or 2.5 percent, are benefiting of the 300-plus that got the drug, but then a substantial number of patients -- well, four -- had a serious adverse event, and two of the patients went to the ICU and had their surgeries delayed. It doesn't

seem rare to me; four serious adverse events seems pretty common, and I think we would expect maybe a bigger benefit for taking on that risk.

I do feel like hospitals should be able to take care of this, but even in these situations under clinical trial circumstances, 2 patients had to go to the ICU, and these are the really good hospitals where patients were getting really good care. So I think that's substantial as far as adverse events.

DR. ROYAL: Thank you.

Dr. Greenberger?

DR. GREENBERGER: Thank you. I wanted to make a few comments from an allergy-immunology perspective. If there's a risk of anaphylaxis, say it could be life threatening, it might be one in 1,000 for a lot of medications. Sometimes it's less than that. Usually it's less frequent than that. But for a media type allergic reaction that qualifies anaphylaxis, we're around 1 percent, and maybe we're three out of 706 because one of the four was actually vasovagal, and that'd be around

1 and 200.

But I would like to go on the record as saying I agree with the agency's warning on slide 92 and slide 94. I thought what was in red was sufficient. I do not think a REMS is indicated or worthwhile. The patient who has received this treatment will have an IV started, her status will be checked, and then the treatment is not given IV push over 10 seconds; it's given over 3 minutes, which is good because, as you saw, the reactions occur with maybe a third or 25 percent of the dose, which is compatible with anaphylaxis.

My point is they're going to be monitored. She'll be monitored for 3 minutes, and then she'll be monitored for 15 more minutes, so it's close to the first 20 minutes. And then as Dr. Dykewicz pointed out, there might be more delayed onset reaction, but she's still going to be monitored in the unit, which is advantageous.

My other point is I think that the understanding of the mechanism of the reaction could come from interested investigators who can

gather samples, but this would be under the post-approval approach, and this would not be something that would have to go into any verbiage. Thank you.

DR. ROYAL: Okay.

Dr. Dykewicz?

DR. DYKEWICZ: Hi. Mark Dykewicz, Saint Louis University. Well, following Dr. Greenberger, I don't have a lot of additional comments. We obviously, again, have evidence that there is a risk for hypersensitivity reaction and anaphylaxis. Only with further experience in a larger number of women will we know what the true incidence of reactions might be and whether there could be some women who would experience reactions beyond the 15-minute bar. But the administration of the agent would be in a setting where there would be ongoing physical presence of personnel who would be able to respond to, for instance, anaphylaxis, should it occur, so I think in that respect, it gives me some solace in terms of risk mitigation.

It brings up, I guess, the theoretical

question about what's the difference between monitoring versus observation, where monitoring might have a higher frequency of vital signs checked, but the the women would be in settings where they would be under observation and able to respond should a reaction occur.

I don't think that a REMS requirement is something that would be necessary, and I think this is a manageable risk because the agent is being administered in settings where people, personnel, should be able to respond to treatment of anaphylaxis with epinephrine. Thank you.

DR. ROYAL: Okay.

Dr. Rosenthal?

DR. ROSENTHAL: Yes. Eben Rosenthal, Vanderbilt, surgical oncology. I definitely agree with what's been said, but I would like to point out a couple of additional things. One is that it is a cancer diagnosis, so when you have a cancer diagnosis, there are some more risks that you're willing to take. So therefore, I do think that no risk is completely acceptable, but the diagnosis is

a life threatening one, conceivably, therefore the risks are somewhat assuaged by that.

The other thing was that the anaphylaxis that occurred seemed to occur, and then there was no sequelae from it. In other words, I know that they were escalated to higher levels of care in ICU, but I didn't get the impression that there was anything beyond that initial change, and even then there were some changes that were very transient, and there was one patient which had a longer sequelae. But given that, I'm sure in the study, they were very cautious, as this is the first time it's happening.

So in terms of the risk, it seems very acceptable and being managed in the environment that we talked about. It doesn't seem like there's an extra certificate that's needed. I would recommend that the patient be awake during the infusion to prevent surgeons from deciding right after intubation that, "Oh wait, I want this to be used," so that if there is a reaction, that it occurs with the patient awake before they undergo

surgery or they're put under anesthesia. And then I think a continued study of the severe events in order to better understand the predisposing factors so that they can be excluded before they get it would be the only post-ad hoc analysis that could be done moving forward. Thank you. That's all I have to say.

DR. ROYAL: Thank you.

Dr. Vasan?

DR. VASAN: Neil Vasan, Columbia. I agree with most of what's been said. I think the risk mitigation and risk assessment is somewhat implicit here because these patients will be getting anesthesia, so I don't think that additional risk management official strategies are necessarily needed.

I will say two things that give me pause are the fact that lumpectomies and breast-conserving surgery is a common procedure. The applicant mentioned the number 180,000, and the number of patients on this trial, as has been already pointed out, was small, so I do think that additional data

will need to be collected. Whether that's through formal postmarketing research by the FDA versus just real-world evidence by the field, I think remains to be seen, but I do think that that will need to be captured. The fact that contrast allergy was an exclusion criteria I think also just needs to be made very clear and that individual breast surgical oncologists will make that decision with their patient. Thank you.

DR. ROYAL: So once again I'll attempt to summarize what I heard. One committee member expressed concern about the adverse events and whether or not they really outweighed the benefits of this technique, but I think most of the committee members felt that the adverse events were manageable and not likely to be life threatening.

We didn't explicitly talk about risk mitigation strategies, but my sense is that everyone agrees with the FDA, the labeling that the FDA is proposing, and that doing some postmarketing research about the incidence of these adverse events would be useful. My understanding is that

the applicant has already agreed to do EPV, which I think would be quite useful, and then there doesn't seem to be any support for the REMS concept. I also didn't hear anything about pretreatment, whether or not patients should be pretreated with anything in order to avoid these adverse events, so I'm assuming that that means that the committee members don't believe that pretreatment is necessary.

Alright. We'll move on to the next question, which is a voting question.

DR. SEO: Dr. Royal, I apologize for interrupting. I believe a couple of panel members still have their hands raised.

DR. ROYAL: Okay. I see one more, Dr. Jacobs and Dr. Greenberger.

Dr. Jacobs?

DR. JACOBS: I was just going to say -- I'm not a clinician, so I can't speak on that part, but the environment that these patients are in is highly monitored, and it seems to me that certainly more investigation of what might be the cause and

whether or not premedication could help would be worthwhile, but I can't see a REMS being appropriate at all. Enhanced pharmacovigilance, that's fairly normal for a newly approved drug, so I think that would be highly appropriate, but given the environment that these patients are in, it seems to just be a little overblown. That's all.

DR. ROYAL: Thank you.

Dr. Greenberger?

DR. GREENBERGER: Having a lot of experience with patients with hypersensitivity reactions, I would just say that practice parameters from organizations might make comments on whether pretreatment might be indicated. And we already heard that 14 women were pretreated, and indeed 1 in 5 people get hives at one time in their life and over 1 percent have chronic hives, which is hives 6 weeks or more.

So a woman coming in with that might well get an H1 antihistamine, but the way the language is, there's no verbiage on that, and I personally am satisfied with, as I said, lines 92 and 94 and

how that's written, so that leaves it up to the physician on hand, and if a patient has to be seen by an allergist ahead of time, that they could work things out.

DR. ROYAL: Okay. Thank you very much.

I'm looking very carefully for any more raised hands. I don't see any, so we'll now move on to the next question, which is a voting question. Jessica Seo will provide instructions for voting.

DR. SEO: Thank you, Dr. Royal.

This is Jessica Seo, DFO, and question 3 is a voting question. Voting members will use the Zoom platform to submit their vote for this meeting. If you are not a voting member, you will be moved to a breakout room while we conduct the vote. After the chairperson reads the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, we will announce that voting will begin.

A voting window will appear where you can

submit your vote. There will be no discussion during the voting session. You should select the radio button that is the round circular button in the window that corresponds to your vote. Please note that once you click the submit button, you will not be able to change your vote. Once all voting members have selected their vote, I will announce that the vote is closed. Please note there will be a momentary pause as we tally the vote results and return non-voting members into the meeting room.

Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Thereafter, the chairperson will go down the list and each voting member will state their name and their vote into the record. Voting members should also address any subparts of the voting question, if any.

Are there any questions about the voting process before we begin?

Dr. Skates, I see your hand raised.

DR. SKATES: Yes. If you vote no, there is

the option of providing recommendations. Is there any option for providing recommendations even if you vote yes?

DR. SEO: I believe Dr. Royal will read the question into the record, and it will detail the rationale or what you can support your vote with if you do vote yes.

DR. SKATES: Okay. Great. Thank you.

DR. SEO: Ms. Pearson, I see your hand raised.

MS. PEARSON: Thanks. This is Cindy Pearson. My question is similar, and I hope this is responsive to your invitation to us to make sure we understand the question, the wording of the question. So that's the spirit in which I'm asking this.

The wording of, "if yes, describe the clinically meaningful benefit and risk mitigation measures that are recommended," I haven't heard any discussion of patient information, which I would like to bring up, and I don't know if I'll be able to bring that up as a risk mitigation measure.

DR. SEO: Okay. So what I'll do is perhaps I will hand it back to Dr. Royal who can begin by reading the voting question into the record and take questions about the wording, and we can get clarification for you on that through that process. Before I do, though, I just want to check if anyone else has questions about the voting process.

(No response.)

DR. SEO: Alright. I do not see any other hands, so I will hand it back to you, Dr. Royal, and we can begin.

DR. ROYAL: So the question is, do the benefits of Lumicell outweigh its risks? If yes, describe the clinically meaningful benefit and the risk mitigation measures that are recommended. If no, provide recommendations for additional data and/or analyses that may support the positive benefit-risk assessment of Lumicell.

So those of you who have questions about what this all means, you can raise your hand, and I think someone from the FDA has their hands raised.

Ms. Tyron [ph]? I guess it's Tyson.

DR. MARZELLA: This is Lou Marzella from FDA. I just wanted to respond to some of the questions that were raised about what happens if you vote yes, can you still make additional recommendations? And the answer is by all means. So you can go ahead and vote, but also when you explain your vote, you can go into the record and explain what additional recommendations you would have.

Is that clear?

(Chorus of yeses.)

MS. PEARSON: Yes. Thank you.

DR. ROYAL: Dr. Pearson?

MS. PEARSON: Yes, that is clear. Thank you.

DR. ROYAL: If there are no further questions or comments concerning the wording of the question, we will now begin voting on question 3.

DR. SEO: We will now move non-voting participants to the breakout room

(Voting.)

DR. SEO: Voting has closed and is now

complete. The voting results will be displayed. There were 16 yeses, 2 noes, 1 abstention, and I'll return the floor to you, Dr. Royal.

DR. ROYAL: 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 include the rationale for your vote. We'll start with the first person on the list, Dr. Richardson.

DR. RICHARDSON: Yes. My name is Andrea Richardson, and I voted yes because the incremental benefits outweigh the small risk of anaphylaxis, and the benefits are mainly avoiding additional surgery.

DR. ROYAL: Dr. Leitch?

DR. LEITCH: Marilyn Leitch. I voted yes, again, because I think while this hasn't gotten to the end game that we want, which is no positive margins, it is an incremental tool that can be used. It'll be most beneficial for surgeons who have the higher re-excision rates, but even for surgeons who have low re-excision rates, they may

have courage to cut back on just random cavity margin re-excision and adopt a more directed approach, which could minimize the amount of tissue that's removed.

I think those of us who deal with blue dye are aware of reactions that can occur with hypersensitivity, so we deal with that and have experience to manage that, and this would be sort of a similar thing to think about for surgeons. So I think it's reasonable and can be applied in a safe way with proper education as surgeons and their staff.

DR. ROYAL: Dr. Vasan?

DR. VASAN: Neil Vasan. I voted yes. There were three co-primary endpoints, two were met and one was not, and the FDA statutes for image and drug approval say that, quote, "Depending on the clinical context, lower sensitivity below 50 percent might be balanced by higher value of the other metric." So since the specificity was 80 percent and the Youden index was 0.36, this was indicative of a non-random benefit, so I felt that

this balance was met.

Regarding the risks, since lumpectomies are de facto performed with anesthesia, risk mitigation and assessment is implicit in the real world, and I do not feel that REMS is needed; however, given that lumpectomies are such a common procedure and the trial was small, I do think that more data are needed to fully understand risk factors and management of AEs. The applicant suggests this through enhanced pharmacovigilance, which is reasonable. It could also be obtained through real-world data.

Finally, this was a complex trial, and I would like to thank the FDA and their biostatisticians for the thoughtful analysis. I would also like to thank the applicant for their excellent presentation, even-handed assessment of the trial data, and frank discussion about adverse event management. Thank you.

DR. ROYAL: Dr. Skates?

DR. SKATES: I voted yes. On balance, I thought that the positives outweighed the

negatives. I was focused on the negatives being additional surgery even though there were false positives. My recommendation is to include in the product insert or product labeling that patient-level metrics be added so that surgeons and patients are clear at the patient level what the benefits are and per-patient benefit what the false positive rate is; how many patients are going to undergo extra, even though it's minimal, additional excisions because of Lumicell. I think that will set expectations that 1 in 10 of those will save a second surgery for a patient and not get people's expectations too high, given that this is a modest benefit, and in my judgment rather minimal downsides. Thanks.

DR. ROYAL: Dr. Hackney?

DR. HACKNEY: I voted yes. I believe that this is an improvement over the status quo. It is better than doing the surgery without having the ability to visualize some areas that are suspicious for residual tumor. So I think it's an improvement, and it will reduce somewhat the number

of people who have to return for a second operation, so I think it's valuable.

I view the risks of the hypersensitivity reactions to be well within the range of many other medications that are routinely used in medicine, and in particular under these circumstances where the patients will be in the hospital in the pre-op area with an IV and being monitored; that if they were to have a reaction, they will be quickly, almost immediately, treated.

I think that the actual effective risk is quite low. It's possible that if they do postmarketing studies, they may find that re-medication is of some value and potentially it might further reduce the risk. So overall, I think the benefits outweigh the risks, and I voted yes.

DR. ROYAL: Dr. Oates?

DR. OATES: Yes. Hi. I voted yes, and the reasons have been articulated already, so I'll be brief. I think having guidance for the surgeon in the OR will be more and more helpful and useful as the technology is rolled out and more and more

surgeons get that experience with the technology. In terms of the risks, in radiology, we see contrast reactions fairly frequently, and as long as the team is aware and is trained to handle any kind of reaction, ranging from hives through anaphylaxis, the patient should be safe.

DR. ROYAL: Alright.

Dr. Pearson?

MS. PEARSON: This is Cynthia Pearson. I voted yes. I voted yes with deep hesitation because the absolute benefit is so low, and almost everyone I've heard talking about the system today has talked about it in a way that could be understood as being much more meaningful or just a larger benefit than it is. The benefit of removing additional cancer is certainly something, but it's speculative. We don't know exactly how much, and the benefit that can be measured of avoiding the second surgery, which is so important to everyone who's undergoing a lumpectomy, is no more than 3 percent in this trial.

So my recommendation, I guess I have to put

it under risk mitigation because that's how this question was framed, but it's really about practitioner and patient education. I believe from what we heard during the open public comment that even highly trained clinicians can overestimate the benefit of this procedure, and I think part of that is based on talking about relative benefit in contrast to absolute benefit.

So my recommendation is that the FDA require that surgeons distribute information in their informed consent procedure that makes the absolute benefit and risk at a patient level clear, and that this information be distributed to patients prior to the day of surgery. So with that caveat, I think the the risk of overclaiming and over-hopefulness, and sort of automatic acceptance of a procedure that women hope will save them from a second surgery, could be tempered to become a more rational and evidence-based expectation of a small benefit. That's my comment. Thanks.

DR. ROYAL: Ms. Fisher?

MS. FISHER: Yes. I also voted yes for many

of the same reasons that have already been articulated, so I won't go into a lot of depth. But I do think that the incremental value we'll get from doing this procedure over time will have some significance. And again, it does provide yet another tool, even if it's just a small advance for now, that could have some significant value for even a few patients, which is very, very important in the whole scheme of things going forward. So I vote yes wholeheartedly. Thank you.

DR. ROYAL: Okay. Dr. Jacobs?

DR. JACOBS: I voted yes, again, for many of the same reasons. I also feel that the benefits, yes, have been somewhat overstated, but in several cases, I think they've been understated. The patients that benefit are 15 percent of those who have positive margins, which is a much bigger number than everybody keeps talking about. I think that's a significant number because only those patients who had positive margins were candidates for second surgeries.

For mitigation, I think that enhanced

pharmacovigilance is a very good idea. I do not believe a REMS would be necessary or relevant. I think that a carefully prepared patient brochure would also be worthwhile so that it would be very clear to the patients that only some patients benefit, what the real risks are, and that it's written in patient language instead of in medical language. That's all.

DR. ROYAL: Dr. Greenberger?

DR. GREENBERGER: I voted yes. I started out from the perspective that the diagnostic agent causes anaphylaxis in 1 percent or 0.5 percent, or somewhere in that range, and is the effectiveness sufficient to account for that and accept it? My answer was yes. While the effectiveness is not my expertise, I've reviewed the papers and listened to the arguments pro and con today, and do state, as was stated, that two or three co-primary endpoints were reached, and that was sufficient, as well as we have sufficient information, as I already said, about what the staff would be expected to be able to do if the immediate reaction occurs. Thank you.

DR. ROYAL: Dr. Rosenthal?

DR. ROSENTHAL: I voted yes, and I do not have any comments to add to what I've already said before. Thank you.

DR. ROYAL: Okay.

Dr. Applegate?

DR. APPLEGATE: Thank you. I voted yes. Justification was already very well discussed. I think while the benefits are incremental, as has been well stated, I think that two of the co-primary endpoints were met, and the other one, while not, was well discussed. So I think that as the surgeons learn this technique, I think we need to offer it, and that in my opinion, in the marketplace, there will be other optical agents that may compete and be improved or this company may improve this agent. The other point I would make is the risk, I think the FDA has provided a reasonable mitigation strategy, so I like the language that was provided. Thank you.

DR. ROYAL: Dr. Dykewicz?

DR. DYKEWICZ: Mark Dykewicz. I voted yes.

I think the balance of the evidence demonstrates that Lumisight provides an incremental benefit in reducing the need for second breast surgery. I think women undergoing breast lumpectomy and their surgeons would still want that incremental benefit to reduce the need for second surgeries. So the benefit outweighs the risk for hypersensitivity reactions in anaphylaxis. I believe the FDA has proposed mitigation strategies that are appropriate, and I think also we have to keep in mind that the agent is going to be administered in medical settings where treatment of anaphylaxis could be given in a timely manner. Thank you.

DR. ROYAL: Dr. Royal. So even though the benefit of this, on average, is quite small, the benefit to the woman who has positive margins that's converted to negative margins because of the use of Lumisight is really pretty great, and the risk from this procedure is certainly very manageable.

Dr. Xiong?

DR. XIONG: I voted abstain I think

primarily based on, number one, the data available; number two, the positive benefit that there is some evidence that is small in magnitude. On the other hand, there are also some risk factors associated with it, and it's also small. So I think the important thing to me is a bigger data set, a bigger trial, so that would be my recommendation.

DR. ROYAL: Okay.

Dr. Dejos?

DR. DEJOS: Hey there. Based on the review of outcomes for the adverse toxicity profile and the limited rate for toxicity for anaphylaxis, as well as those minor cases of extravasation and nausea, I do think that the safety profile of this agent does appear appropriate or minimal, so it doesn't really cause any major concerns from my perspective. So therefore, I vote yes.

DR. ROYAL: Thank you.

Dr. Bolch?

DR. BOLCH: Yes. I voted yes on this question for many of the reasons previously stated. The benefit is marginal but important for the

individual patient. Also, there was a lot of positive statements made by breast surgeons that we had heard from, and that made an important impact on me. And yes, there are risks, but they seem to be very manageable. Thank you.

DR. ROYAL: Dr. Burstein?

DR. BURSTEIN: First, I want to thank FDA for obviously always doing a great job preparing all these materials. I thought the presentations by the investigators were excellent. I thought the presentations by the patient advocates and other supporting people were focused and well done as well, so thank you for organizing a very successful program.

That said, I voted no. I think that FDA is looking for an answer on what is usually called clinical validity; does the test do what it says it's supposed to do? Does it find residual cancer? Which I suppose it does. But then everything is couched in terms of clinical utility; does it make for a better outcome for the patient?

There's really no data here that that's true

in this trial. This was not a randomized trial in the conventional sense of comparing two arms for outcomes; it was essentially a large, open-label experience, using the drug or the dye contrast agent and software in an experience to see what the outcomes would be without any expectation of comparing to those who did not receive this; and in that small study, there were 8 patients out of 357 who might have not had a second operation.

It's very important not to have unnecessary surgery, we all get that, but as the investigators know well, decisions about re-excision are far more nuanced than just margins. There are people who have positive margins who do not have re-excisions. There are people who have negative margins even in their actual study, if you look at the flowchart, who do have re-operations. So it's a subtle and small difference at most, and I don't think you can say that this reduces the risk of re-operation. I would encourage FDA to monitor any marketing or advertising very carefully. That is not what the FDA asked us to decide, and if they approve it,

it's not what the indication is for. You can't say that it lowers it.

The investigators themselves understand this. In their New England Journal of Medicine evidence paper that was published last year, they said, "The findings suggest potential benefits in terms of reduced rate of surgery and potential improvements in healthcare costs" -- we don't know if that's true either -- and they thought this benefit merited evaluation and future trials.

I confess I'm with them on that point. I think it's a great technology. I'd like to see a well-conducted, large, randomized, phase 3 study with the endpoint of re-operation. I think you'll never see a difference in local recurrence rates because of multimodality therapy, but that would really prove the usefulness and benefit of the intervention in my mind. Thank you.

DR. ROYAL: Thank you. Dr. Griffin?

DR. GRIFFIN: Yes. Marie Griffin, Vanderbilt. I completely agree with that assessment, and I don't have a lot to add, except

that I would be very enthusiastic about future clinical trials that could either show a reduced rate of re-excision and/or a change in need for radiotherapy.

DR. ROYAL: Okay. So I will summarize what I've heard the committee members say. The majority of committee members voted in favor of approval of this agent. The committee members that had more reservations really were concerned about what sort of meaningful effect this might have on patient outcome, and obviously this study doesn't really inform us about that. So that would be my summary of our discussion. Before we adjourn, are there any last comments from the FDA?

(No response.)

Adjournment

DR. ROYAL: I guess I need to look at whether anybody has their hand raised, and not seeing anyone with their hand raised, we will now adjourn the meeting. Thank you.

(Whereupon, at 5:05 p.m., the meeting was adjourned.)