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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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VIRTUAL PUBLIC WORKSHOP – STUDY DESIGN CONSIDERATIONS FOR TRANSBRONCHOSCOPIC THERMAL ABLATION DEVICES FOR THE TREATMENT OF OLIGOMETASTASES TO THE LUNG

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M E E T I N G

(11:00 a.m.)

DR. EYDELMAN: Good morning. It is my great pleasure to welcome all of you to this workshop on Study Design Considerations for Transbronchoscopic Thermal Ablation Devices for the Treatment of Oligometastases to the Lung.

My name is Malvina Eydelman. I'm the Director of the Office of Ophthalmic, Anesthesia, Respiratory, ENT and Dental Devices at the FDA's Center for Devices and Radiological Health, known as CDRH.

CDRH's vision is for patients in the U.S. to have access to the high-quality, safe and effective medical devices of public health importance first in the world. To that end, today's workshop is the result of extensive collaboration with stakeholders in the medical device ecosystem. I want to acknowledge the diligent preparation by the respiratory team in my office, with tremendous support from FDA staff at CDRH and other centers within the Agency.

We're particularly gratified by the enthusiasm and collaborative spirit of the many clinical experts in the fields of medical oncology, radiation oncology, thoracic surgery, interventional radiology, and interventional pulmonology, who will share their clinical knowledge and experience during this 2-day workshop.

I want to extend a special thank you to the patients who have agreed to share their experiences about what it is like to live with oligometastases to the lung and its treatments. Patients are the center of everything we do here in CDRH, and we look forward to learning from them at this afternoon's session dedicated to the patient perspective.

By combining the best internal and external talent, we hope this workshop will deliver transformational change, shortening the time from conception to market.

It is my privilege to now introduce Dr. William Maisel, who is the Director of the

Office of Product Evaluation and Quality.

(Pause.)

DR. EYDELMAN: Dr. Maisel, please unmute yourself.

(Pause.)

DR. EYDELMAN: I understand we're having some technical difficulties with connecting Dr. Maisel, so for now I would like to ask Dr. Brandon Blakely to proceed, giving us an overview of the regulation of these devices.

Brandon.

DR. BLAKELY: Hello, everyone. And thank you for attending this virtual public workshop regarding appropriate regulatory approaches to ensure the safety and effectiveness of transbronchoscopic thermal ablation devices, or TTA devices for short, a novel local therapy for the treatment of oligometastasis to the lung, which we will abbreviate as OML.

My name is Brandon Blakely, and I am the Assistant Director of the Respiratory Devices Team in the Office of Health Technology 1 in the Center for Devices and Radiological Health.

Here is an outline of what I will present this morning. I will begin with a broad overview of FDA and medical device regulation in the United States; the regulatory background of thermal ablation and their use in the lung and the emergence of these novel TTA devices for treatment of OML; challenges identifying appropriate clinical validation strategies for TTA treatment of OML, leading into the main questions the Agency has for the clinical community motivating this workshop.

First, I'll begin with an overview of FDA. FDA has a broad responsibility for promoting and protecting public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply,

cosmetics, and products that emit radiation. We want to speed innovations that improve medical products and want to ensure that the public gets the information they need. In terms of organization, the Agency is composed of several centers responsible for a particular class of product.

Focusing on medical products, the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, and the Center for Devices and Radiological Health are responsible for biologics, drugs, and medical devices respectively. There are also combination products that combine drugs, devices, and/or biologic products with the lead center being determined by the primary mechanism of action.

I'm now going to focus on CDRH's role regulating medical devices. For a medical device to be legally marketed in the United States, the FDA requires a reasonable assurance of safety and effectiveness by weighing any probable benefit to health from the device's use against any probable risk of injury or illness from such use.

Devices are regulated in three risk-based classifications. Low-risk and well-understood devices are classified as Class I, where there is an assurance of safety and effectiveness through general controls. General controls apply to all medical devices and include fundamental requirements that devices are not adulterated or misbranded and that manufacturers follow quality system manufacturing regulations. Most of these devices are exempt from premarket review by FDA.

Moderate-risk devices are considered Class II devices for which safety and effectiveness can be assured through special controls. Special controls are usually device specific and include things like performance or labeling requirements. These devices usually require premarket clearance through the 510(k) process.

Finally, higher-risk and generally novel devices including implanted devices or those intended to sustain life are Class III devices which usually require a premarket approval, or

PMA.

Shown here is an overview of the types of premarket applications that FDA reviews depending on the regulatory pathway. For Class II devices going through the 510(k) process, the manufacturer has to submit a 510(k) notification in which they demonstrate substantial equivalence to a predicate device. A predicate device is another legally marketed Class I or Class II device that has the same intended use and similar technological characteristics in which the new device can be demonstrated as having similar or substantially equivalent safety and effectiveness.

Novel devices can be brought into the market in two mechanisms: de novo requests for low- to moderate-risk devices and PMAs for high-risk devices. If a device is not substantially equivalent to a legally marketed predicate and the device is appropriate for Class I or Class II classification, a sponsor may request a de novo. Such devices should be sufficiently understood, such that all risks can be appropriately mitigated through general and/or special controls to provide a reasonable assurance of safety and effectiveness. If the de novo request is granted, these devices could serve as predicates for future devices cleared through the 510(k) process.

PMA devices have higher risk and uncertainty. These devices require valid scientific evidence to demonstrate a reasonable assurance of safety and effectiveness. Valid scientific evidence is typically clinical.

Finally, Class III devices that can treat small populations and meet other criteria may also be brought to market under a humanitarian device exemption, or HDE. Unlike PMA requirements for a reasonable assurance, the review standard is for safety and probable benefit.

FDA's premarket review is not solely focused on technology. Equally important is intended use. The term "intended use" means the general purpose of the device or its

function and encompasses the indications for use. The term "indications for use," or IFU, describes the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended. The IFU should be sufficiently detailed to inform what information may be needed in support of a premarket review so that FDA can evaluate the safety and effectiveness for a given indication. The IFU is critical to determine the appropriate clinical study design, the clinical reference standard, and the context of use.

I'm now going to shift from the general FDA regulatory framework to discussing the particular regulatory background for TTA devices subject to this workshop. Technologic antecedents of these devices are percutaneous devices, needle electrodes, antennas or transducers inserted through the body during image-guided, minimally invasive procedures. The needles can irreversibly destroy tissue by delivering different types of energy including, but not limited to, high frequency ultrasound and radio or microwave frequencies.

Reported clinical applications of thermal ablation catheters include a variety of organ systems and conditions including atrial fibrillation, bleeding, chronic pain, and destruction of solid malignancies, for example, those in bone or liver, and as general surgical tools for tissue ablation and coagulation. However, these devices have not been approved or cleared specifically for ablation of lung parenchyma or malignancy in the lung soft tissue.

As listed here, there have been several published reports of clinical use of these technologies for treatment in the lung, although these devices are not cleared or approved specifically for ablation of lung parenchyma. It is important to note that FDA does not regulate the practice of medicine. Treating physicians are not bound to FDA-approved labeling when prescribing, administering, or providing treatment using regulated medical devices.

Although thermal ablation of lung parenchyma has not been cleared or approved, this does not preclude this use as a practice of medicine for individual patients when determined to be in the best interest by the knowledge and judgment of their physician.

However, in 2007, FDA did release a public health notification resulting from several reported deaths following RF ablation of lung tumors. In this statement, FDA clarified that the Agency has cleared many radiofrequency ablation technologies as tools for general ablation of soft tissue by thermal coagulation necrosis. These devices have also been cleared for certain specific indications including partial or complete ablation of non-resectable liver lesions and palliation of pain associated with metastatic lesions involving bone, but they have not been cleared specifically for lung tumor ablation.

Over the past several years, we at FDA have been working with several manufacturers seeking to introduce to the U.S. market advanced iterations of thermal ablation devices. These devices utilize flexible microwave ablation antennas that can be delivered through a bronchoscope. Recent advances in imaging, navigation, and robotic bronchoscopy has generated interest in utilizing these approaches to detect small sub 3 cm sized nodules in the lung and accurately target and ablate them using a natural orifice and potentially avoiding the complications with percutaneous methods.

Ablation of oligometastasis to the lung, or OML, has been proposed from multiple stakeholders as a potential intended use of these platforms. Much more detail will be provided in Session 1, but in brief, oligometastasis is broadly defined as the stage between locally confined cancer and widely metastatic disease for which locally treating the limited metastatic lesions may potentially extend life or be even curative. The proposed intended use of these devices in the U.S. market is as another means to locally treat oligometastatic disease to the lung.

When evaluating novel technologies or an intended use, FDA makes regulatory

determinations based on a benefit-risk paradigm. Since treatment of OML would be considered a new intended use, these devices would not have a legally marketed predicate to enable application of the 510(k) process. Instead, these devices would require a regulatory pathway for which FDA could determine that there is a reasonable assurance of safety and effectiveness by weighing probable benefit against probable risk.

However, when beginning to consider the potential benefits as weighed against potential risks of this procedure, FDA was faced with numerous difficult questions with no universal clinical consensus.

First, there are different definitions of oligometastatic disease, including OML. Also, patient prognosis is not based solely on the number of lesions but on the primary histology, timing, and detection of OML, response to systemic or other local therapies, and many other factors. In the context of this unclear definition of OML, it is not clear what factors should be relied upon to determine if a patient is a good candidate for treatment with TTA.

Furthermore, as will be discussed in later sessions of this workshop, a growing body of evidence suggests that local consolidated treatment of oligometastatic nodules may lead to better clinical outcomes as compared to systemic therapy alone, including overall survival. However, much of these data are derived from studies of local consolidated therapy achieved by surgery or radiation with much less evidence for percutaneous ablation.

It is unclear if technical efficacy (i.e., the ability to successfully ablate targeted nodules) of these TTA platforms could be correlated with longer-term oncologic benefit based on extrapolations from studies of local control with other modalities. Therefore, it is unclear if some measure of local control of treated lesions is sufficient benefit to demonstrate a reasonable assurance of safety and effectiveness.

Other potential endpoints, such as quality of life, are difficult to identify since

nodules in the lung parenchyma no larger than a few centimeters are usually asymptomatic.

Finally, in addition to the uncertainty regarding the most appropriate endpoint, the complex and heterogeneous nature of the patient population and disease will pose challenges for clinical study design, particularly randomizing comparable treatment versus control groups.

As an alternative, FDA has considered proposals for single-arm studies with statistically matched historical controls. However, how to appropriately define a priori relevant parameters by which to match historical controls is challenging, and quickly evolving standard-of-care treatments may undercut the relevance of many historical controls.

Finally, as will be discussed by Dr. Drezner in the next talk, many traditional oncologic benefits, like overall survival or progression-free survival, are time-to-event analyses, which are meaningfully measured in randomized controlled trials.

We must also consider the risks of these devices and how those risks should compare to other treatment options.

Equally as important, we are seeking input from patients who could benefit from these technologies, to hear their stories and learn what benefits are most meaningful to them for their recovery.

In summary, to answer these important questions, we need to ensure appropriate clinical study design to obtain data demonstrating a reasonable assurance of safety and effectiveness of treatment of OML using TTA devices.

We are holding this public workshop in order to invite the clinical community, patients, manufacturers, and the public to discuss relevant information for assessing the benefits and risks of these TTA devices for treatment of OML. In order to facilitate the entry of these devices to the market, we are hoping to understand the emerging consensus

on the role of local therapy and the management of OML and how the safety and effectiveness of a new local therapy such as TTA should be evaluated.

We hope this workshop can help address several important scientific and regulatory questions raised during our review of this emerging technology as a possible treatment to meet this urgent clinical need for more options for OML.

What specific criteria should be considered when determining whether a patient with OML is likely to benefit from treatment with TTA?

What endpoints constitute a sufficient benefit to demonstrate a reasonable assurance of safety and effectiveness, local control or longer-term clinical endpoints such as overall survival?

Finally, what is an appropriate level of safety of these emerging local control modalities, and how should safety and risk be evaluated during clinical validation?

We are delighted to hold this workshop to address these important questions, and we thank the patients and clinicians for attending and sharing their perspectives.

We would like to acknowledge all the effort throughout the Agency to help organize this workshop in CDRH, many people in OHT 1, with specific special thanks to Drs. Christopher Eger, Logan Budd (ph.), Eric Mann, and Malvina Eydelman, for their contributions to the content of this presentation, and guidance and support from OHT 4, OHT 7, OPEQ immediate office staff, particularly Jeanne Oxley, and the Office of Communication and Education, Tracy Gray and the Patient Science and Engagement Team with the patient perspective panel. From the start, we have also worked very closely with the Oncology Center of Excellence, particularly Dr. Nicole Drezner, who will now discuss clinical trial endpoints for the approval of cancer drugs.

DR. MAISEL: Hi. Good morning, everyone. Thank you for your patience with some of our technical difficulties this morning. I'm Bill Maisel, Chief Medical Officer at FDA's

Center for Devices and Radiological Health, and Director of CDRH's Office of Product Evaluation and Quality.

Today begins an important 2-day workshop for us, as you know, related to the study design considerations for transbronchoscopic thermal ablation devices for the treatment of oligometastasis to the lung and, as it's been mentioned already, bringing this community together really underscores FDA's commitment to fostering the development of important new technologies to help patients, and I think Brandon has already outlined some of the unique challenges of this device space and some of the questions we have.

And our approach to this technology and this disease state is really similar to what we've done over recent years, we've taken numerous steps to help bring important new technologies to patients. We've published numerous policies to support the availability of safe and effective medical products. We've focused on striking the right balance between premarket and postmarket data collection. We have strengthened the U.S. clinical trial enterprise with a focus on early product development and first-in-human clinical trials, and we've frequently engaged with and collaborated with stakeholders in forums just like this one, to ensure that we're listening, to ensure that we're developing policies that are thoughtful, balanced and, most importantly, meet patient needs.

These approaches and actions have had a measurable positive impact. Over the past decade we've decreased the time to full clinical trial approval for medical device studies by more than 90%. That means clinical trials get started more quickly, and for products that work, it means patients get access to them more quickly. We've seen a fourfold increase in the annual number of novel medical devices authorized for the U.S. market.

And patients remain at the heart at what we do, and I'm sure you feel the same way. Many individuals and many stakeholder groups play critical roles in the evaluation and the communication related to the benefits and the risks of medical products, but patients live

with their medical condition, they make daily choices regarding their health care, and their voice and their perspectives are really critical to understanding the impact of medical products on their health and wellbeing.

For this reason, we routinely strive to incorporate the patient perspective into our work: what clinical outcomes are meaningful to them, what do they care about, what product risk profile are they willing to tolerate, how effective does the product need to be. And this is not some academic exercise. Our approach to product development and evaluation clearly has a meaningful impact on patients and, importantly, as you've already heard, part of today's workshop will focus on the patient perspective.

We're also grateful to have the participation of so many attendees during this 2-day workshop, and we look forward to hearing your ideas and perspectives. We believe there's great value in bringing together stakeholders to solve shared challenges, to leverage collective experience and opportunities, and to achieve a common outcome of developing and bringing to patients safe and effective products. In fact, we believe this is the most effective and most efficient way to make meaningful improvements in patient care, that is to work collaboratively, to work together.

Today we'll have the opportunity to hear not only the patient perspective, but also from medical professional societies, from product manufacturers, from healthcare providers, from researchers, and from colleagues from across FDA's medical product centers, and we look forward to these productive discussions and your input. I very much want to thank you for being here.

And now I will turn it over to Dr. Nicole Drezner so that we can hear more regarding the regulatory considerations for other therapies intended to treat oligometastasis to the lung. Thank you.

DR. DREZNER: Hi, good morning. My name is Nicole Drezner, I am an oncologist and

I am the team lead of one -- of the Thoracic and Head and Neck Malignancies Team in the Division of Oncology 2 in CDER. Thank you so much to my colleagues in CDRH for organizing this workshop and for giving me the opportunity to speak. Next slide, please.

Today I will be giving a regulatory perspective on study design considerations for ablation devices intended for the treatment of patients with pulmonary oligometastases as seen through the lens of development of oncology drugs and biologics. I will give a brief overview of oligometastatic disease in the lung and its unique biology, as well as the varied modalities used to treat oligometastases. I will also give a general overview of oncology study designs for drugs and biologics with a focus on those that are intended to support registration of a drug product, and of the study endpoints that are supportive of the different types of regulatory approval.

This summary of our experience in regulating drugs and biologics is intended to provide our perspective for the consideration of the types of study design that will support approvals of ablation devices for the treatment of patients with oligometastases to the lung. Next slide, please.

Oligometastatic disease is generally referred to as being confined to a limited number of organs classically assessed in the patient as one to five metastases in one or more organs. Since the term was coined in 1995, it has been hypothesized that the oligometastatic state is a distinct clinical entity existing between completely localized and metastatic disease rather than an earlier time point on a continuum between the two.

There is biologic and translational evidence supporting this concept of a more indolent disease state that may relate to cancer cell specific properties and their ability to survive outside the primary organ.

Clinical data describing the improved long-term survival of patients with various oligometastatic solid tumor types receiving local therapies relative to the overall survival

rates for patients with metastatic disease in the same tumor types also supports the notion that oligometastatic disease is a clinically distinct entity affecting a proportion of patients who may be cured by local therapies.

The Kaplan-Meier curve on this slide shows the long-term overall survival results from the stereotactic ablative radiotherapy COMET study in which patients with a controlled primary tumor and one to five metastases were randomized to receive either SABR to all sites of metastatic disease or palliative radiotherapy. After a median follow-up time of 50 months, of 51 months, the primary outcome measure of median overall survival was 50 months in the SABR arm compared to 28 months in the control arm, corresponding to a hazard ratio of 0.47. Although this study has some limitations, particularly in the inclusion of patients with multiple different tumor histologies, it provides some supportive evidence for the treatment of patients with oligometastatic disease with local therapies. Next slide, please.

However, there are few large-scale randomized trials comparing the modalities employed for the treatment of oligometastatic disease to the lung. Surgical resection has historically been considered the gold standard treatment with reported overall survival rates of 26% and 22% at 10 and 15 years. However, due to the ineligibility of many patients due to age, physical condition, or tumor location and potential short-term morbidity from surgery, less invasive therapies such as SBRT or ablation therapies are accepted options for patients unable to undergo surgery.

Similar overall survival rates to surgery have been reported for SBRT, although there are few head-to-head trials evaluating the two. However, rates of post-RT pneumonitis, particularly in the era of immunotherapy and the limits on re-radiation to tissues, may be improved upon by thermal ablation technologies, particularly in that these may preserve lung function and allow for re-ablation of the same lesions.

Relatively high rates of pneumothorax have been reported with these technologies and there may be a higher local recurrence rate with ablation technologies compared to SBRT. However, this has not been formally studied in large prospective randomized trials.

Furthermore, much of the published literature describing the effect of ablation technologies focuses on local efficacy alone, assessed by rate of complete ablation or short-term rates of local recurrence or provides long-term outcomes on survival without a randomized comparator arm. Next slide, please.

There are several types of trial design considerations for the development of drugs and biologics for the treatment of cancer that differ based on the tumor types and prevalence, intent of the study, and extent of clinical trial data already available for the proposed indication.

As per the Code of Federal Regulations, the FDA approves drugs based on substantial evidence of efficacy from adequate and well-controlled investigations. Studies must allow a valid comparison to a control and must provide a quantitative assessment of the drug's effect. The most reliable method for demonstrating efficacy is to show a statistically significant improvement in a clinically meaningful endpoint in a randomized controlled trial.

However, in studies where there is no available therapy and where major tumor regressions can be presumed to be attributed to the tested drug, the FDA has accepted overall response rate, or ORR, and response duration observed in single-arm studies as substantial evidence supporting accelerated approval in some settings, and as supportive of regular or traditional approval in some rare or biomarker-driven tumor types.

However, because of the variability in the natural history of many forms of cancer, single-arm trials do not adequately characterize time-to-event endpoints such as overall survival or disease-free survival or event-free survival or progression-free survival.

Finally, a non-inferiority trial should demonstrate the new drug's effectiveness by

showing that the new drug is not less effective than a standard regimen by a pre-specified amount or non-inferiority margin. The standard regimen should have a well-characterized clinical benefit such as a survival benefit. Non-inferiority trials rely on externally controlled or historical data to establish the active control's treatment effect size. These trials, however, usually involve large sample sizes compared with superiority trials and involve replication of clinical trial results. Next slide, please.

There are several oncology endpoints, including overall survival, DFS/EFS, PFS, ORR, and patient-reported outcomes, that can serve different purposes for regulatory approvals and provide either evidence of direct clinical benefit or a demonstrated effect on an outcome known to predict clinical benefit based on the specific context of use. In general, in oncology drug development, we consider direct clinical benefit to be an improvement in the way a patient feels, functions or survives.

However, the determination of the appropriate endpoint to support an approval is based on the specific disease under study and is highly dependent upon factors such as effect size, effect duration, available therapy, disease setting, location of disease, the clinical consequences of delaying or preventing disease progression or a delay in administration of more toxic therapies and the overall risk-benefit relationship.

The table shown on this slide includes several commonly used oncology study endpoints and whether they provide evidence of direct benefit or are known to predict benefit.

DFS/EFS, PFS, and ORR have served as both types of endpoints depending on the factors listed on the slide. For each of the time-to-event endpoints listed and for PRO or patient-reported outcome endpoints, randomized trials are required to demonstrate an effect on the outcome versus the control. Not mentioned here are landmark event rates such as OS rates, as these are generally not considered clinically meaningful, given that they

represent only one point on the survival timeline and may be misleading. The log-rank test that is used for hypothesis testing in randomized trials uses all the information in a survival curve, as do hazard ratios. Although median overall survival is frequently reported, it is considered in the context of all of the survival information and gives a general understanding of how two populations compare. Next slide, please.

Traditional or regular approval refers to the longstanding route of drug approval based on the demonstration of clinical benefit or an effect on an intermediate or surrogate endpoint known to predict clinical benefit. This is distinguished from accelerated approval, which is associated with the use of an intermediate clinical endpoint that is reasonably likely to predict clinical benefit to support drug approval. As a condition of accelerated approval, the drug sponsor must conduct clinical studies to verify and describe the actual clinical benefit.

In oncology, one of the commonly used endpoints for an accelerated approval is overall response rate, which allows for the conduct of single-arm trials and for an earlier measurement of the treatment effect. However, response rate has also supported traditional approvals in certain circumstances, including for rare cancers, those with long natural histories, and those for which a randomized trial would lack clinical equipoise. For example, crizotinib and entrectinib received regular approval for the treatment of patients with a ROS1-positive non-small cell lung cancer based on the observation of response rates of such magnitude and durability that it would not have been feasible to randomize patients to the previous standard of care of platinum-based chemotherapy. Next slide, please.

In summary, local control endpoints, which have been reported in the literature for ablation technologies, have not yet been validated as early measures of clinical benefit for any cancer type in studies of drugs or biologics.

Landmark event rate endpoints, such as OS rate, are generally not considered

clinically meaningful and are uninterpretable without access to patient-level data for propensity score matching.

Although endpoints such as overall response rate can be evaluated in the setting of a single-arm trial, these are generally not considered suitable to demonstrate evidence of direct clinical benefit except in rare circumstances.

Although overall survival is the gold standard oncology endpoint for the evaluation of drugs and biologics, benefits in EFS or DFS have also supported traditional approvals of oncology therapies and are only evaluable in the setting of a randomized clinical trial.

These concepts may be useful when considering trial design types and choice of endpoints for studies of thermal ablation technologies. We recognize the inherent differences in development of oncology drugs and devices, but in the treatment of the same patients there is significant intersection between the two. I look forward to the discussions over the next 2 days. Next slide, please.

Thank you so much, in addition to my colleagues at CDRH, to my colleagues in the Oncology Center of Excellence, DO2, and the Thoracic and Head and Neck Malignancies Team.

I would now like to introduce our next session, during which we will hear statements from the various professional societies representing the skilled and dedicated clinicians who provide care to patients with oligometastatic disease to the lung. We will be hearing from the following professional societies who will be presenting in alphabetical order: AABIP, AATS, ASCO, ATS, ASTRO, STS, and SIR. Thank you.

DR. WAHIDI: Good morning. Can you hear me? All right. All right, let me share my screen. Good morning, everyone. My name is Momen Wahidi, I'm a Professor of Medicine at Duke University School of Medicine and the Director of Interventional Pulmonology and Bronchoscopy, and I'm here on behalf of the American Association for Bronchology and

Interventional Pulmonology (AABIP). Thank you for inviting us to represent our members and our society.

Just a quick background. The AABIP was founded in 1992 and it aims to advance the field of bronchology and interventional pulmonology, and enhance the care of our patients and alleviate their suffering. We are committed to developing, implementing, and disseminating evidence-based knowledge, techniques and skills.

This is our general approach to new technology. We typically want to understand the unmet needs being addressed by the new technology, evaluate the existing data and assess the need for additional research, balance the benefits with the adverse events and the cost of the technology, and then educate our members via guidelines or publications in the *JOBIP* or *Journal of Bronchology and Interventional Pulmonology*.

As far as the topic at hand today, transbronchoscopic thermal ablation for oligometastatic disease to the lungs, as it was just reviewed, the current standard of care for the most part includes surgical resection for selected patients or stereotactic body radiation therapy (SBRT). We do believe that local therapy options may provide additional local control or be the primary treatment if the standard of care is not feasible.

Our main considerations for a new technology, particularly a transbronchoscopic thermal ablation technology, are the following: We want to learn about efficacy compared to the standard of care. We want to learn about patient selection factors such as age, performance status, histology, number and location of metastases, and prior and current treatment. We believe patient selection is critical to the success of this proposed treatment. We also want to learn about the safety, the overall safety, of this proposed technology particularly in relation to location of the lesion near major vessels, airways, and other thoracic bio-organs. And finally, once this is approved by the FDA or if it's approved by the FDA, as an organization that cares about the members and the patients, we want to

be involved in training and competency for these new techniques.

And I'll end here.

DR. YASUFUKU: Thank you very much for giving me the opportunity to speak today. My name is Kazu Yasufuku, I am currently the chief of the Division of Thoracic Surgery at the University of Toronto. I will be speaking on behalf of the American Association for Thoracic Surgery.

Oligometastasis is defined in the literature as patients with up to five metastases in no more than three organs and a maximum of three lesions per organ.

Temporal patterns include synchronous, where the primary cancer is in place at the time of discovery, and metachronous or recurrent, where primary cancer has been previously treated and controlled.

Oligometastasis to the lung is most frequently seen in patients with colorectal cancer, renal cell carcinoma, and sarcoma. Since there is a low burden of disease in such cases, unlike patients with extensive metastatic disease, if the primary disease is well controlled, local therapy can be considered for lung tumors if all lesions can be completely treatable.

Based on the evidence and recommendations from various medical societies, treatment options for oligometastasis to the lung include surgical resection, SBRT, and image-guided thermal ablation. While surgery may be preferred when feasible, treatment depends on multiple factors including the location, size, prior therapy, patient preferences, physiological reserve, and local expertise. The decision of treatment options should be made at multidisciplinary cancer conferences.

There is growing evidence in multiple clinical trials regarding the role of SBRT for lung tumors with excellent outcomes comparable to surgery. For the sake of time, I will not go into details.

For thermal ablation, radiofrequency ablation is where most data is available for the lung. There is more experience with microwave ablation in other tumors, but we are seeing increasing adoption of this technology for lung tumors. There's extensive experience in endobronchial palliation using cryoablation, but still very limited experience for treatment of lung tumors.

This slide shows the outcomes of CT-guided radiofrequency ablation for early-stage lung cancer and lung metastases. Various studies show excellent local control using RFA. Similar outcomes have been reported for CT-guided microwave ablation with excellent results.

So the question is why consider bronchoscopic ablation? As mentioned, SBRT is the standard of care for medically inoperable patients with lung cancer or a lung tumor. However, some patients are not candidates due to tumor location, prior radiation, or existing lung disease. Percutaneous CT-guided ablation is associated with relatively high morbidity.

Now, different bronchoscopic technology is becoming available to navigate to peripheral lung nodules. Bronchoscopic approach may be safer and cost effective. There is also a possibility of one-stop shop, thus diagnosis, lymph node staging, and treatment at the same time.

Possible ablative technology for bronchoscopic ablations are listed here. There is still a very limited number of reports on the use of RFA, microwave ablation, and direct tumor injection. Other ablative approach is still under investigation. In general, there is lack of evidence for these promising technologies.

Technical requirements for performing a successful bronchoscopic ablation include accurate navigation to the target, confirmation of access or real-time monitoring during ablation, flexibility of the ablation system and understanding of the ablation zone.

Various bronchoscopic navigation methods are available to reach out into the periphery. Most recently, robotic bronchoscopy is a technology that is slightly different from the other existing technology.

At the Toronto General Hospital we use the hybrid operating room that has the cone-beam CT as well as the CT scan. This is helpful for real-time monitoring of ablation and also monitoring of intraoperative complications.

In summary, local therapeutic options for patients with oligometastasis to the lung should be determined in a multidisciplinary fashion.

New ablative modalities may become an alternative therapeutic option to SBRT in medically inoperable patients.

Various bronchoscopic navigation modalities will be required to assess the peripheral lung tumors accurately in a minimally invasive way.

Ongoing and future multicenter clinical trials, including ABLATE and RESECT studies, will be very important to understand the safety and effectiveness of different ablative technologies and to build the evidence.

Thank you very much for your attention.

DR. MALDONADO: Hello, my name is Fabien Maldonado. I am a Professor of Medicine, Thoracic Surgery, and Mechanical Engineering at Vanderbilt University in Nashville, Tennessee. I'm also a faculty at the Vanderbilt Center for Biomedical Ethics and Society, and I will be speaking on behalf of the American Thoracic Society on the topic of this virtual workshop, which is bronchoscopic thermal ablation for the treatment of oligometastases to the lung.

My disclosures are as follow and I have outlined those that I think are most pertinent to this particular topic.

And I will start by saying that I think there's great rationale for consideration of

bronchoscopic thermal ablation in the context of oligometastatic disease. Some of the potential advantages or theoretical advantages of bronchoscopic ablation include the possibility, in the same setting of the ablation procedure, to confirm the histology of the lesion that is being targeted. We can also stage the mediastinum, potentially in the same setting, as well, things that are not possible with transthoracic approaches or SBRT, obviously, which is radiation therapy.

This procedure bronchoscopically could also potentially help in acquiring tissue for molecular analysis, which may help in terms of adjuvant treatment. It's presumably a lung-sparing treatment compared to surgical resection, for example, which is currently considered the standard of care.

It's an alternative to the alternative to surgery in the context of repeat SBRT, so patients who have already benefited from SBRT that may not be candidates for repeat SBRT, and also as an alternative to radio-resistant tumors that may not be amenable to SBRT treatment.

And one major advantage that has been proposed is that bronchoscopic approaches may help in terms of safety by mitigating the problem of pneumothorax, which is quite high with transthoracic or percutaneous approaches.

Now, there are obviously a lot of downsides with bronchoscopic approaches. The main one is the reason why this FDA virtual panel is convened today, which is that we have little to no data on safety and efficacy. But there are, I think, also a number of potential issues such as the fact, for example, that to this day we do not have great data on the occurrence of bronchoscopy in reaching peripheral targets in the lung and even in the context of modern bronchoscopy, with robotic bronchoscopy, cone-beam CT guidance, that accuracy is modest at best and certainly not well published in the literature.

Another potential downside, I think, that's important to consider is that approval for

oligometastatic disease, of bronchoscopic thermal ablation, would almost immediately lead to off-label treatment of early lung cancer, for which we would not have any data, at least, initially.

So when we think of a potential study design for bronchoscopic ablation studies to establish the safety and efficacy of the procedure in a compelling way that could potentially inform management and benefit patients, I think there's a number of possibilities, but here are three possible designs that I think have been considered.

The first one is the so-called ABLATE and RESECT study, where you're going to ablate the targeted lesion and then the patient is going to go to standard-of-care surgery and you get the perfect assessment of local control histologically. The issue with this is that, of course, we don't have any long-term safety data as patients have gone through surgery after the ablation, so we don't know what the potential for complications of the bronchoscopic ablation procedure really is.

The other issue is that it is difficult to recruit patients for this type of design. Most patients with suspicious lesions who are planned to go to surgery are not going to be inclined to get an ablation procedure solely for the purpose of advancing science and that's completely understandable.

The second potential study design, then, is another single-arm study where the ablation is followed by some assessment down the road of local control based on imaging, and I think that's a reasonable study design with the caveat that in order to judge the efficacy of the treatment, we really have to rely on comparison with historical controls and there comes the issue of not having a good gold standard for local control with imaging endpoints, and that's a potential problem.

Now, if we establish a standard in terms of local control endpoint and we compare to an arm that's a little bit different than what is being proposed, and what I think is

probably the most reasonable study design to consider in this particular context, which would be a randomized trial randomizing patients to SBRT, which is the "standard of care" alternative to surgical resection, which is the standard of care for oligometastatic disease, versus transbronchoscopic ablation procedure looking at the same endpoint in both arms so we have both safety and efficacy data at the end of the day.

So I'll follow the so-called PICO format to talk about patient interventions comparison and outcomes to briefly finish this short presentation with some potential ideas for future study design.

In terms of patient, I think the focus on oligometastatic disease is reasonable with the caveat that I already mentioned, that approval would almost certainly lead to off-label use for primary/early lung cancer, which again would be done without evidence to back it up. And so that's a potential downside of the focus on oligometastatic disease.

Now, obviously, the definition of oligometastatic disease will need to be critical, I think, for the purpose of a study looking at this, a single-arm metastasis should be targeted, and I think that patients should be declined for or decline standard-of-care surgery, patients should not be candidates because of respiratory indications or simply decline to have surgery and then they should be offered participation in this trial, which would randomize them to SBRT versus transthoracic -- I'm sorry, transbronchoscopic ablation procedure.

Now, I think for the purpose of safety it would be good to consider having a central adjudication for selection of patients based on an independent panel that will review the scan and decide whether targeting this particular lesion is a good idea or not, and this panel should be composed of interventional pulmonologists, radiation oncologists, and thoracic surgeons, for example, and that's a suggestion, obviously.

In terms of intervention, it goes without saying that transbronchoscopic thermal ablation should be performed by experienced interventional pulmonologists or thoracic

surgeons with a robust track record of successful navigation and/or robotic bronchoscopy. I think it should include tissue confirmation before treatment, no matter what the modality of treatment is, whether it's SBRT or transbronchoscopic ablation and mediastinal and hilar lymph node sampling, if clinically indicated. And I think for the purpose of the study, at the very least, cone-beam CT confirmation of the optimal positioning of the ablation probe in the lung tissue is absolutely critical.

In terms of comparison, what are we going to compare the bronchoscopic ablation to? I think SBRT seems to be the logical candidate. Given the variability of local control endpoint definitions and the heterogeneity of diseases included, I think we need to have a direct comparison. Having historical controls, I think, is going to be of limited value and would ultimately not serve our patients as best as possible.

Since SBRT is established as safe and effective, and bronchoscopic ablation, of course, the potential additional benefit, a non-inferiority study design might be considered showing that transbronchoscopic ablation procedure is non-inferior to the established SBRT and may actually be enough in that with bronchoscopy, as I pointed out earlier, we have the benefit of histologic confirmation and potentially mediastinal staging in addition to acquisition of tissue for molecular analysis, if needed.

Finally, the outcome should be an imaging-based local control endpoint. That remains to be defined and, in my opinion, should be centrally adjudicated by two independent and blinded chest radiologists with a third radiologist as a tiebreaker, if needed. Now, there's a number of secondary endpoints that could be considered, as well, such as progression-free survival, overall survival, safety, lung function, additional procedure, if needed, and cost.

And I will finish here. I thank you very much for the attention and for the opportunity to speak on behalf of the American Thoracic Society. Thank you very much.

DR. STERMAN: Good afternoon. My name is Dr. Daniel Sterman from NYU Langone Medical Center in New York City, and I'll be speaking on behalf of the American Society of Clinical Oncology regarding bronchoscopic ablation of oligometastatic malignant pulmonary lesions.

These are my disclosures.

Once again, I think that we need to start with a definition of oligometastatic disease to the lung. The concept of oligometastatic disease has emerged to identify a stage of limited spread of malignancy to lungs from approximately one to five metastatic sites, from either intrathoracic or extrathroracic sources, in which local administration of definitive treatment may improve survival.

The most substantial evidence regarding the effectiveness of local treatment in patients with oligometastatic disease to the lung is reported from a surgical series in metastatic colorectal carcinoma. Treasure et al., for example, described several years ago survival rates of between 40 and 60% at 5 years among patients having pulmonary metastases resected for advanced colorectal carcinoma. However, thoracic metastasectomy may be challenging for patients with marginal lung function, poor general condition, or refusal of surgery. And these concerns are especially notable for patients with multi-lobar involvement in which there are multiple metastases in different lobes of the lungs bilaterally.

The histology of the oligometastatic disease may also be important. I think that we need to avoid initial treatment of tumor types that have an expected brisk response to systemic therapy, such as multiple metastases to the lung of EGFR mutant adenocarcinoma, small-cell carcinoma, and ER-positive/PR-positive breast cancer, for example, that may respond to targeted therapies, chemotherapy, or hormonal therapy.

There are a variety of minimally invasive approaches that have been used as part of

the standard of care for treatment of oligometastatic disease to the lung. Obviously, we mentioned robotic surgery, video thoracoscopic surgery to resect a certain number of nodules in patients with metastatic disease. As you heard recently from Dr. Maldonado in his presentation, SBRT has also been used to target specific lesions with good effect. And percutaneous ablation using a variety of technologies, radiofrequency, cryotherapy, and microwave, has been used to treat oligometastatic disease to the lung.

But it should be remembered that surgery offers local control only, there is no effective surgery on distant disease, that SBRT and percutaneous ablation have complications and side effects including relatively high rates of pneumothoraces in percutaneous ablation and the risk of radiation pneumonitis with SBRT. And SBRT requires repeated treatments, often three to five treatments per site, potentially, and has significant cost, as do some of the other interventions.

And we have to figure out what the ultimate goals of the treatment are. The goal should be prolongation of survival, as many of these lesions are not causing palliative issues, and so palliation is not an important initial goal of treatment. Cure may be possible, particularly as part of multimodality therapy. And ultimately, because of some of the certain characteristics of the ablative technologies, there may be synergy with systemic immunotherapies that will be very important as we assess these technologies.

Bronchoscopy has historically a role in the therapeutic management of oligometastatic pulmonary malignancy. At present, you can use bronchoscopy to localize peripheral cancers to guide radiation therapy, like SBRT. You can use bronchoscopy, including guided technologies such as with electromagnetic navigation or robotic bronchoscopy, to guide surgical approaches to make them more lung-sparing. In the future, we'll be able to deliver therapeutic agents directly using bronchoscopy. For the purposes of today, we're talking about thermal ablation and in the future we may be combining thermal

ablation with both drug and thermal ablation combinations.

Now, as we're doing bronchoscopic ablation, we have to be mindful of what the goals are. We need to ablate lesions which are both readily accessible as well as difficult to access, which is why imaging modalities to confirm device in lesion will be so important.

We need to have the capacity to do a complete ablation in a single procedure which might require multiple angles to be able to ablate from a bronchoscopic approach.

We need to have the capacity to treat multiple lesions, potentially at one sitting, to be an advantage over other types of technology which can only target one lesion at one sitting.

We need to make sure that we have a penumbra effect with a negative margin, which will be equivalent to that achieved with other ablative technologies and to some degree, equivalent to what surgery is achieving.

We need to show a lower complication rate that we've seen to date with percutaneous ablation, which will be one of the major comparators.

And we need to potentially show an in vivo vaccine effect, that is, a generation of both local and systemic anti-tumor immune responses by this ablation to justify potential synergy with systemic checkpoint inhibitor.

In terms of design of clinical trials of bronchoscopic ablation for oligometastatic disease, we should think about inclusion criteria. Again, based upon our definition, patients should have confirmed tumor histologies with less than five lesions in the lung parenchyma which are refractory to, or ineligible for, standard-of-care treatment such as surgical resection. Patients have to have adequate cardiopulmonary function to tolerate the ablation procedure and they have to have target tumors amenable to bronchoscopic access using guidance techniques, including potentially robotic technologies with the use of adjunctive imaging such as augmented fluoroscopy and/or cone-beam CT to confirm device

in lesion prior to ablation.

In terms of exclusion criteria, we should exclude patients who are eligible for standard-of-care treatments. For example, surgical resection of localized oligometastatic disease in a patient with good pulmonary function, that should be done prior to consideration of bronchoscopic ablation.

Patients who have inaccessible lesions to bronchoscopic access and/or lesions adjacent to high-risk structures in the thorax, such as pleura, intra-lobar fissures, and pulmonary vessels, in which the risk of ablation would exceed the potential benefit.

And then patients with severe impairments of cardiopulmonary function and/or uncorrectable coagulopathies would be among those who should be excluded from consideration.

In terms of trial designs, I think that there have been a number of Phase I studies or first-in-human studies already performed in which the primary endpoints have been appropriate, which are safety and feasibility and demonstration of device in lesion and the ability to complete the ablation.

In terms of safety, I believe that safety has to be shown to be superior to percutaneous ablation in terms of pneumothorax, hemoptysis, and effusion, as well as superior to SBRT in terms of injury to the local lung.

Secondary endpoints of early-phase clinical trials should include tumor response by RECIST at 1, 3, and 12-month time points and exploratory endpoints should include abscopal effects, that is, a demonstration of responses in tumors that have not been targeted by the initial ablation, as well as looking at biomarkers of systemic immune response induced by the bronchoscopic ablative technology.

Phase II designs, I believe, can be done with single-arm Phase IIa propensity matched historical cohort comparisons with a primary endpoint likely being progression-free survival,

because the response rates may not be well demonstrated by RECIST because of the presence of scars, especially early on in the process after the ablation.

Secondary endpoints can be to a response by RECIST, but I think these ultimately will not be the primary endpoint by which we're going to be evaluating this technology.

Ultimately, a Phase III design, I think, should be a randomized controlled trial of bronchoscopic ablation in combination with systemic therapy versus systemic therapy alone, with treatment of one or more targets to be a part of a specific design. It is also possible that we could design comparisons of a randomized controlled trial with direct comparison to another ablative technology such as percutaneous ablation or to SBRT.

The primary endpoint likely should be overall survival, although PFS may also be an endpoint that we should be looking at in Phase III designs.

So in terms of the future of bronchoscopic ablative treatments of malignant pulmonary disease, I think obviously the ultimately goal would be complete ablation of multiple tumors with guided bronchoscopy in a single setting. We should be able to treat one or more metastatic sites in combination with other adjunctive technologies, meaning that we may use surgery, SBRT, percutaneous ablation, local immunotherapy in combination with bronchoscopic ablation. Designing these trials that combine different modalities will be much more difficult, I think, but ultimately may be more "real world" in terms of how they will be applied to patients.

And lastly, I do believe that once we develop these types of trials for bronchoscopic ablation of oligometastatic disease, that we will then be looking at the same types of interventions in earlier-stage primary lung cancer.

Thank you very much for the invitation and the time to speak.

DR. IYENGAR: My name is Puneeth Iyengar and I'm a thoracic radiation oncologist at UT Southwestern Medical Center. I will be giving ASTRO's consensus statement for the FDA

oligometastatic-to-the-lung workshop.

These are my disclosures.

ASTRO is an organization that was founded in 1958 with the main purpose to advance the practice of radiation oncology through multiple different mechanisms. Today, as the premier radiation oncology society in the world, ASTRO has more than 10,000 members.

The therapeutic role for local therapy in the management of metastatic disease has historically fallen on the side of palliation. But work over the last few decades has suggested that local therapies in metastatic disease may actually be used to improve durable tumor control, progression-free survival, and maybe overall survival.

The concept of oligometastatic or limited metastatic disease was developed by Hellman and Weichselbaum in the 1990s. They describe "The evolution of metastatic capacity to have an intermediate state in which spread may be limited to specific organs and metastases might be present in limited numbers."

This diagram demonstrates what they were talking about. Initially, a patient may present with localized disease. Over the course of time, that localized disease may spread to one or two or three spots in the body and then eventually, the disease may spread beyond those few oligometastatic spots and the spread and the oligometastatic nature of disease could be present at the time of initial diagnosis, represented by synchronous disease or after initial treatment, as described, metachronous oligometastatic or oligoprogression disease.

Coinciding with the idea of oligometastatic disease was the evolution of stereotactic body radiation therapy. This is the use of high doses of radiation using image guidance to treat disease with limited number of fractions, and the advantages of SBRT is that it's noninvasive as compared to surgery, no surgical side effects or postoperative recovery, and

ultimately stereotactic body radiation therapy can be used to treat metastatic disease very quickly and to nearly all anatomical sites in the body.

Over the course of multiple decades, the use of SBRT was evaluated in the setting of oligometastatic disease, and it was clear that the program and the approach was feasible and potentially beneficial to metastatic disease to different parts of the body.

Since the idea of oligometastatic disease has evolved, ASTRO's three main publication venues, *Advances in Radiation Oncology, Practical Radiation Oncology*, and the *International Journal of Radiation Oncology - Biology - Physics*, has published more than 1200 articles and presentations describing the use of SBRT and other forms of radiation in the approaches for treating oligometastatic disease. So clearly, ASTRO and radiation oncologists have an exquisite understanding of the potential role of local therapy in the form of radiation, and then management of both oligometastatic disease and oligometastatic lung disease.

Certainly, because of this, ASTRO has led the way in outlining the relevance of oligometastatic disease and the relevance of local therapy since the Hellman and Weichselbaum definition of oligometastatic disease. Many critical papers, as I've just described on the subject, have been presented at the ASTRO annual meeting or in ASTRO-sponsored journals.

But ASTRO believes that one cannot simply view oligometastatic disease as limited to the lungs. Oligometastatic disease is relevant potentially to all primary cancers and must be discussed with respect to whole body distribution. Only then can one identify whether a local therapy is necessary, sufficient, and/or beneficial.

With that perspective, only one local therapy has the ability to treat nearly all sites of metastatic disease in the body: external-beam radiation therapy, especially in the form of SBRT, also known as stereotactic ablative radiotherapy, or SABR. These forms of treatment

can deliver safe, effective and noninvasive radiation therapy to nearly all relevant oligometastatic disease from all primaries. Furthermore, use of SBRT does not delay patients from returning to or freshly receiving systemic therapy, which is really the main treatment modality for all metastatic patients. Even in the setting of recent findings with renal cell carcinoma, for instance, there's even early evidence to suggest that oligometastatic patients may not just benefit from radiation as an adjunctive therapy but in fact, as the only therapy.

It is with this understanding along with the idea that the larger Phase III studies for use of local therapies for oligometastatic disease have not been completed, and we think that local therapies including radiation should be used after a multidisciplinary discussion for oligometastatic disease of distinct patients. At the end of the day, oligometastatic disease to the lung or oligometastatic lung disease is but one of many locations that this spectrum of disease may land, requiring a close examination of the entirety before making a judgment of the uses and benefits of local therapy.

When you think about surgery versus radiation: cold steel versus hot fire. Surgical experiences for metastasectomies were older and more established, but as we established that SBRT is safe and very effective in terms of tumor control and versatile in terms of anatomy and localization of utilization, radiation may take a bigger role in oligometastatic disease management. Furthermore, no downtime between SBRT and systemic therapy presents itself on a common basis.

Much less data, especially prospective and randomized, exists for RFA. Now, there are good studies for primary lung, head and neck, nasopharyngeal, prostate, breast, etc., using SBRT or XRT for local treatments of oligometastatic disease.

So at this time, we believe that local therapy should not yet be standard for oligometastatic disease but should be used during treatment on clinical trials or as part of

the multidisciplinary approach if no trial exists.

So how should we really define oligometastatic disease? Is it three mets versus five mets, is the number even relevant? I think the consensus at this stage is three to five mets would be appropriate.

Does the location of mets matter? Potentially, yes. Some disease sites lead to worse prognoses than others.

Does the volume or size of mets matter? No. Most lesions can receive SBRT.

And should patients with N1 or N2 disease be included? Yes, but because there's a need to treat the primary disease.

Do we know the optimal sequencing to use local therapy? More than likely, patients should be treated in consolidation or at oligoprogression, that's where we have most of the data.

What is the right overall metric to assess local therapy that benefits? Conservatively, I would say the most optimal metric is overall survival.

Ultimately, we need to finish larger Phase III studies to really get a consensus on how important local therapies are and when they should be employed.

And this is why it's very important. SBRT practice patterns suggest that most, if not all, radiation oncologists also use SBRT for oligometastatic disease. So we need the data to ensure that what they're doing is most helpful and beneficial to patients.

Thank you very much.

DR. MITCHELL: Good morning and afternoon. My name is John Mitchell, and I'm a thoracic surgeon at the University of Colorado presenting on behalf of the Society of Thoracic Surgeons. STS is pleased to participate in this FDA workshop examining optimal trial design for transbronchoscopic thermal ablation of pulmonary oligometastatic disease. Additionally, the society recognizes the importance of participation by all relevant clinical

stakeholders in this workshop, and we commend the FDA for the structure and organization of this virtual meeting. Next slide.

Oligometastatic disease involving the lungs remains a vexing clinical problem. Current treatment strategies depend on several factors, including the number and location of metastases, various oncologic factors such as histology and disease-free interval, various patient comorbidities, and finally, the local expertise of available therapies at the treatment site. Next slide.

Broadly speaking, modern treatment strategies for oligometastatic disease include surgical resection, stereotactic radiotherapy, percutaneous ablation or some combination of these. All of these therapies are associated with complications and other factors which limit their use.

The ability to treat oligometastatic disease with transbronchoscopic thermal ablation would potentially represent a major therapeutic advance. When doing so, it will be essential to have thoracic surgeons involved in the care team. Evaluating treatment options for individual patients and providing guidance on the sequencing of therapeutic interventions to ensure patient safety, combined with the ability to mitigate postoperative complications, will be critical. Next slide.

Limited data are currently available regarding the use of this technology, specifically through a transbronchoscopic route. Accordingly, STS advocates that initial trial design focus on prompter patient selection, patient safety, and efficacy of the intervention, factors that will be addressed in some detail later in this meeting. Input from thoracic surgeons will play a key role in this discussion.

Further, we hope that initial trial designs allow for development of helpful adjuncts in treating patients with this modality, such as appropriate radiologic surveillance following treatment. Next slide.

Cancer registries, as currently designed, are not equipped to capture data on transbronchoscopic thermal ablation of pulmonary oligometastatic disease. Systematic data collection will be key to trial design and assessment of new treatment paradigms such as TTA.

STS has significant experience in clinical registries and systematic data collection. It would be desirable to leverage our strengths with the STS general thoracic surgery database to form a registry tracking clinical information as these trials progress. The success of the STS/ACC TVT registry, which now has over a half a million patient records, partnering with FDA, industry, payers, and other stakeholders, provides a potential blueprint. Collection of real-world evidence has proven to be a powerful tool, and the TVT registry is a successful model to bring stakeholders together to facilitate advancement of new technology and answer important clinical questions going forward. Next slide.

Finally, there would be a natural inclination to extend these trial designs developed for pulmonary oligometastatic disease to other clinical problems such as early stage non-small cell lung cancer. Without adaptation, such a leap would be a mistake. The differences in presentation, extent of disease, management, and prognosis mandate a completely fresh look at the use of TTA for primary lung cancer.

The STS appreciates the opportunity to participate in this workshop and we look forward to the discussion over the next few days. Thank you.

DR. SOLOMON: Hello, my name is Stephen Solomon. I am the Chief of Interventional Radiology at Memorial Sloan Kettering Cancer Center. Today I come to you as the representative from the Society of Interventional Radiology, the society who has over 8,000 members who practice image-guided therapies to treat patients around the world. Today we are talking about lung ablation for oligometastatic lung disease.

Here are my disclosures.

Interventional radiologists play a critical role in lung ablation. We use advances in imaging that have taken place over the last several decades that allow us to see right inside a patient and pinpoint where a particular cancer is. We couple that with advances that have taken place in engineering, that have developed tools such as microwave ablation, cryoablation, and radiofrequency ablation, that allow us to take a needle and place it into the cancer, kill the cancer with heat or cold and allow the body to naturally remove the dead tissue and avoid an incision that might have complications and lead to longer hospital stays.

Interventional radiologists have played a critical role in developing the ablation technology over the past 30 years. We've used benchtop research, animal model research, and eventually clinical research to demonstrate the value of this technology. Here are some pictures of some of the translational research that has been done. Today, hundreds of thousands of patients around the world have been treated since the development of ablation technology.

Our goal is to transform cancer surgery. Instead of one that is an open procedure with its concomitant potential complications, we want to transform it into one that uses advances in technology to pinpoint exactly where a cancer is and then burn it and destroy it.

We use advances in imaging, as I've said. Here is an example of CT fluoroscopy, near real-time imaging where we can pinpoint a small lung cancer and target it with this ablation needle to perform an ablation.

Here's another patient, where you can see what it looks like when the needle has been inserted into the lung cancer just prior to turning on the energy.

And here's what it looks like over a sequence of imaging, PET/CT scans for three and a half years after the ablation. You can see what it looks like initially, where there's activity

on the PET scan. The activity disappears over time. The CT scan shows the original nodule and then it shows a scar over the three and a half years after ablation.

In one particular study that was performed with nine patients who had oligometastatic disease, after radiofrequency ablation the patient was resected 2 to 4 weeks later and you can see that in this particular study there was no viable tissue after resection, demonstrating the success of this technique.

In a paper that our group published several years ago, we looked at colorectal cancer and oligometastatic disease and we were able to show successful local control of 80 to 90%. But I want to emphasize one other particularly important topic, and that is giving a patient a chemotherapy holiday. If you are able to treat all of the oligometastatic disease, many medical oncologists may take a patient off their chemotherapy and give them a break, something that improves quality of life, and it should not be ignored when we think about trials that involve ablation therapy.

Our success with lung ablation over the past 20 years has led to societies such as the Thoracic Surgery Society, in a webinar on oligometastatic disease, recognizing the value of lung ablation. But further, the NCCN guidelines have incorporated it as part of the standard treatments for kidney cancer, colorectal, sarcoma, and even primary lung cancer. So lung ablation is an accepted treatment and, as I said, thousands of patients have been treated with it.

We, as interventional radiologists, are very intrigued by the transbronchial approach. We believe we can perform this successfully using imaging. In a swine study that was multi-institutional, we were able to identify a target in this pig, we were able to use imaging alone without a robot or bronchoscope, and we were able to target exactly where that lesion was and place the ablation needle right into it. And you can see the sheath, you can see it moving, and then you can see the confirmation in the multi-plane oblique imaging. And you

can see how we use that sheath to target the lesion and then we're able to drive the microwave antenna through the sheath, into the lesion, perform the ablation and, as I say, confirm it with cone-beam CT. And finally, you can see that on pathology we successfully ablated the target lesion, demonstrating the success of this treatment.

I just want to summarize and say that lung ablation for oligometastatic disease has been a proven technology that has been used for over 20 years and is part of international guidelines, including the NCCN guidelines.

Interventional radiologists with skills in both imaging and thermal ablation have played an important part in the development of this treatment.

New transbronchial ablation techniques require further investigation, but interventional radiologists should play an integral role in this technology's evaluation.

And I thank you for the time that you've given me to speak to you today on this topic and I'm available for further questions should you have any. Thank you.

DR. BLAKELY: Thank you, Dr. Solomon, and to all the other speakers.

This is Brandon Blakely, Assistant Director of Respiratory Devices in CDRH. We will now hear statements from two manufacturers who have both publicized the breakthrough device designation status from FDA for transbronchoscopic thermal ablation of malignancies. We will be hearing from the following manufacturers in alphabetical order of the speakers: Dr. Jen Mattingley from Medtronic and Dr. Mark Soberman from Johnson & Johnson. Thank you.

DR. MATTINGLEY: Hello, I'm Dr. Jen Mattingley. I'm the senior medical director of the lung health business at Medtronic where we are committed to our mission to alleviate pain, restore health, and extend life. I want to thank the FDA and workshop participants for their commitment to developing appropriate frameworks for studying transbronchoscopic thermal ablation devices in the oligometastasis-to-the-lung patients, and for paving a path

to bringing a needed therapy to this underserved patient population. As manufacturers, FDA participants, as well as workshop participants, we are all united in the same goal of bringing safe and effective therapies to improve patients' lives.

Today our presentation will cover the limitations of our available local treatments for OML, and highlight the role of TTA to address the unmet need of patients with OML within the care continuum. We will discuss appropriate study designs and endpoints for demonstrating effectiveness of TTA, and we will also highlight some safety considerations.

First, let's talk about oligometastatic disease to the lung. OML is a widely understood disease state that is intermediate between localized cancer and widespread metastatic disease. These patients are very unique in that they all have Stage IV cancer, but also have the potential for significant life extension or even cure if local effective therapies can be provided to all their metastatic lesions. Because of the life-threatening nature of Stage IV cancer, it is imperative to respect patient choice when selecting therapies, both with systemic or local options.

There is a definitive unmet need in patients with OML. Although there are currently two widely accepted local treatment options, surgical resection and SBRT, both have limitations and side effects that need to be considered by patients and their care teams.

Surgical resection is considered the gold standard, but at the cost of reduced lung volume and pulmonary function. Some patients may be unable to physically withstand the procedure and with any surgical procedure, there's considerable postoperative pain and activity limitations that may not be acceptable to all patients who are considered eligible for surgery.

Although SBRT is generally well tolerated by patients, there are also short and long-term risks and side effects that may not be acceptable to all patients. This procedure often requires multiple sessions at specialized facilities which may not align with the OML

patient's values and wishes.

We want to acknowledge that OML patients can have a complex presentation. Let's envision a scenario where there are two separate metastatic lesions in the upper lobe of the left lung and a third metastatic lesion to the lower lobe. In this particular case, the two lesions in the upper lobe are peripheral and would be amenable to surgical metastasectomy. The third lesion, however, is deeper in the lower lobe and although could be potentially surgically resected, it would require taking a large amount of lung tissue and may be more amenable to SBRT as a form of local control.

OML treatment decisions cannot be just defined by number and location of lesions, as we will discuss in the following slides.

I want you to imagine that we have three patients that all have the exact same pattern of disease with those three lesions that we previously discussed in the left lung. I want to introduce you to Carol, Marie, and Rosa. While their presentation of cancer is identical, in all three patients the local therapy may provide significant life extension or even a cure. The decisions for treatment also depend on the patient's individual preferences and health status. Let us consider the other factors that impact these three patients and whether the existing local treatment options that we have available today meet their needs.

I'd like to introduce you to Carol. She is a healthy 48-year-old who has had no previous lung surgery and has excellent lung function. She, because of her age, prefers a very aggressive treatment plan and so together with her care team, they have opted to do surgery for the two upper lobe lesions and SBRT to the lower lesion. Carol has choices today that meet all of her needs and preferences.

Next I'll introduce you to Marie. Marie is a 62-year-old female who has a history of mild COPD and had a previous lobectomy in her right lung to treat an earlier lung

metastasis. Given Marie's wishes to pursue any treatment that could prolong her life, she has opted with her care team to undergo SBRT to all three lesions in her lung, as surgery was not recommended due to her previous lobectomy. Her care team acknowledges that SBRT may further reduce her lung function, but Marie wants the most established, aggressive pathway that is available to her even if her lung function worsens. Today, Marie has all the choices that meet her needs.

Lastly, I would like to introduce you to our third patient, Rosa, who's also a 62-year-old female. But unlike our previous patient, Rosa has a history of more severe COPD and stable cardiac disease. Rosa is not eligible for surgery due to her lung function, and her care team does suggest SBRT but acknowledges that that would further reduce her lung function. Rosa is wanting to extend her life, but her top priority is to maintain her current quality of life so that she can travel with her husband and enjoy quality time with her young grandchildren. Therefore, she declines the offer to undergo SBRT. Rosa is not left with any local therapy choices that meet her needs.

Medtronic is committed to addressing this unmet need and providing more options to patients like Rosa. As we have discussed previously, current local therapy choices do not meet the needs of all OML patients.

TTA has the potential to provide a local treatment option with the following possible advantages: the procedure is minimally invasive and can be completed in a single treatment, it utilizes the same technology as percutaneous ablation devices which have been shown to have selected the image of tumor tissue with the aid of intraoperative CT imaging, protect healthy lung tissue, and the ability to repeat ablations if local progression ensues. An important point to remember also is that TTA can be used in conjunction with other local options or systemic therapy.

While there are associated risks, they are expected to be less than the more invasive

therapies. Potential side effects of TTA include pneumothorax, airway bleeding, unintended tissue thermal injury, and generalized risks associated with the anesthesia and bronchoscopy.

Clinicians who have already used TTA outside of the United States tell us that this therapy provides a valuable option in their treatment arsenal for patients like Rosa and others for whom surgery and SBRT are not good choices.

A direct quote from Dr. Kelvin Lau at St. Bartholomew's Hospital in London states, "Patients with malignant lesions in the lung often have limited therapy options due to lesion locations, comorbidities, and treatment side effects. The results from the NAVABLATE study explore the potential benefit of a more individualized treatment for patients and offer a new option for surgeons and physicians to provide a minimally invasive, localized treatment of malignant lesions in the lung."

Now that we've addressed the unmet need, let's turn our attention to appropriate study designs and endpoints for demonstrating the effectiveness of TTA.

It is critical to distinguish between the data required for FDA marketing authorization and the data required for widespread clinical acceptance or inclusion into clinical guidelines. The FDA has traditionally not required clinical data for local therapy such as SBRT, and in some cases has only required clinical data showing a local effect in treating tumors. The study elements proposed are thus consistent with FDA requirements for similar devices.

It is important to make sure that these devices are available in the near term to allow for further study by the clinical community to help better inform treatment guidelines.

The approach to study design and endpoints needs to be informed by the therapy's role in the care continuum, and should also consider the full body of evidence available

related to local therapies in OML.

Multiple studies have shown that when effective local therapy is added to systemic therapy, there is a statistically and clinically significant increase in survival.

As can be seen in this table, it is well established in the literature that local therapies demonstrate a benefit to overall survival when used in conjunction with systemic therapy. While these are relatively small studies, there is a consistent finding in size of benefit. We also know the same is true for progression-free survival as reported in the literature.

Medtronic believes strongly that premarket clinical studies should be designed to show that TTA provides durable, effective local control of OML lesions. Demonstration of durable local control provides objective evidence of benefit in this patient population and is consistent with least burdensome principles. Given the full body of evidence that exists, a more efficient design is in the best interest of OML patients.

Because these Stage IV patients should be given maximum autonomy in their treatment decisions, and they may select multiple local treatments, local control of the treated lesions is a more suitable primary endpoint than overall survival or progression-free survival.

Appropriate study designs and endpoints for demonstrating effectiveness of TTA can be derived from previous studies of SBRT. Data from the extensive literature on SBRT can be used to establish a performance benchmark for showing that TTA devices, in fact, provide effective local control. If TTA provides a similar level of local control to that achieved by SBRT, then it is appropriate to infer that TTA will provide the same survival benefit as has been documented for SBRT. Local control is an appropriate surrogate endpoint for improved survival in this patient population.

Local control can be demonstrated through objective radiologic measurements that show lack of progression in each ablative lesion and the level of metabolic activity in the

treated area. As an objective response rate, local control is amenable to being studied in a single-arm trial.

Follow-up through 12 months is sufficient to investigate the effect of local ablation therapy in patients with oligometastatic cancer and limited alternative treatment options for the following reasons: 12 months is approximately the median survival in patients with OML treated only with systemic therapy; 12-month disease-free interval has also been shown to be an independent predictor of recurrence in patients undergoing surgical resection for OML from colorectal cancer in a study by Onaitis.

The majority of adverse events would also be captured in this time frame as adverse events such as pneumothorax or airway bleeding are acute and present within the first 30 days of the procedure. Acknowledging there have been past questions about safety of ablation in the lung, there are some risk mitigations that can help ensure safe use of TTA moving forward.

Current microwave products have provided more predictable ablation zones and thermal effects than historical devices.

The transbronchial approach eliminates the need for a pleural puncture and in some cases can reduce the amount of vasculature and healthy lung parenchyma that are exposed to physical and thermal effects from the ablation device.

Effective training and labeling can be used to ensure overall procedural safety.

A study conducted under the oversight of the FDA and IRBs will ensure that there is appropriate patient selection for TTA.

Encouragingly, three OUS studies of the Emprint TTA technology have reported no Grade 4 or 5 adverse events through 56 patients.

We would now like to think about a potential future state that might exist when the first TTA device is available on the U.S. market supported by the types of clinical data we

have suggested here. Let's assume that the clinical study showed a high level of local control of OML lesions in a single-arm study similar to a rate of control reported for SBRT devices. Let's also assume that the safety data from the study showed a relatively low rate of adverse events needing medical intervention and that most patients returned to normal activities the next day. How might this TTA treatment option affect the choices made by our three patients I introduced you to earlier?

Let's recall Carol, Marie, and Rosa. Carol's care team may not even discuss the new option with her because she is such a good candidate for the existing local therapies. And likewise, Marie's care team may discuss an option of TTA, but she still may opt for SBRT because she wants to choose a more prudent treatment option consistent with her desire to treat her cancer aggressively. Rosa's care team would likely discuss this new option with her, since she is not a surgical candidate and is reluctant to undergo SBRT. We believe that Rosa may be interested in TTA as a treatment option that can provide a high probability of controlling her lung lesions with only minimal effect on her current quality of life.

With TTA as an available local treatment option in addition to surgery and SBRT, all three patients' needs are now met.

Once again, we would like to thank the FDA and the speakers and panel members for their efforts to help define the appropriate framework for studying TTA in the OML patient population. We look forward to continuing to engage with the FDA to meet our joint goal of bringing a much needed additional therapy option to OML patients. Thank you.

DR. SOBERMAN: My name is Mark Soberman, and I am the Senior Safety Officer for Ethicon Global Surgery at Johnson & Johnson. My colleagues at J&J and I appreciate the opportunity to participate in this FDA virtual public workshop.

On this slide you see our proposed agenda and the speakers for today's presentation.

Patients with oligometastatic disease, or OMD, are different than those with widely metastatic disease. This is an intermediate state of metastatic disease with a smaller number of tumors and those tumors are amenable to localized therapies. The definition is up to five lesions in no more than three organs, a maximum of three lesions per organ, and the primary disease must be controlled. Now, oligometastatic disease to the lung, or OML, is OMD with lung involvement.

In my clinical practice as a thoracic surgeon over some 20 years, I evaluated and operated on countless patients with oligometastatic disease to the lung. I vividly recall one of my patients with metastatic osteosarcoma. She was a brilliant young woman who presented when she was an undergraduate pre-med student. After limb-sparing surgery, she develop metastases to the lung. Over the years, she underwent several metastasectomy procedures and was able to finish her undergraduate degree. She was accepted to medical school and I had the distinct honor of being at her white coat ceremony and placing her white coat upon her for the first time. Sadly, though her life was extended for several years, she succumbed to her cancer.

Now, to be a candidate for local therapy regardless of modality, the primary tumor must be controlled and all metastatic lesions must be completely treatable so that an R0 result can be obtained. We believe that there is an opportunity to address a critical unmet need for patients with OML by providing patients with an alternative therapy that provides benefit while reducing risk.

The goal of local therapy is to eliminate all measurable disease, rendering the patient NED, or no evidence of disease, which is a great emotional and psychological benefit. Local therapy can extend life in this group of patients. A study of surgical metastasectomy demonstrated a 5-year survival of 36% in patients who had a complete R0 resection versus 13% in those who underwent an incomplete R1 or R2 resection. There is

substantial observational data showing a survival benefit, although those data are somewhat mixed, and many patients successfully eradicated in the known sites of disease allows for reduction or avoidance of the toxicity associated with systemic therapy. And patient choice is important. Patients want to make informed decisions about their disease management and understand their options. Local therapy is recommended by the NCCN guidelines and is included in consensus and position statements by various professional specialty societies.

Local therapy can be achieved with multiple modalities. The evidence suggests that there is equipoise across all three modalities: surgery, SBRT, and thermal ablation. We conducted a systematic review and meta-analysis of studies evaluating OS in mets patients with thermal ablation or SBRT and saw a 3-year survival of around 50%. Pooled data from nine large metastasectomy studies demonstrated a similar OS, or overall survival, of around 50%, which is consistent with multiple citations demonstrating a 3-year OS of 40 to 60% after metastasectomy in these patients.

Now, as we consider the options for local therapy, it is important to note the overall trends towards less invasive therapy in numerous disease states. The increasing utilization of TAVR for aortic valve disease and PCI for coronary disease are just two examples.

I will now transition to my colleague, Dr. Balaji Laxmanan.

DR. LAXMANAN: As an interventional pulmonologist, I have a witnessed the growth of bronchoscopic techniques and, more importantly, I have had the pleasure of seeing the benefits that these new approaches have brought to my patients. You know, bronchoscopy was once a rarely considered diagnostic procedure. With the development of endobronchial ultrasound, thin bronchoscopes, navigations and techniques, the incorporation of external imaging and now robotics has allowed interventional pulmonologists and thoracic surgeons to diagnose and stage lung tumors in a very safe,

effective, accurate, and incision-less manner. And there is immense excitement from both practitioners and patients around the potential that new and novel endoluminal therapies could have in treating lung tumors.

Robot-assisted transbronchial thermal ablation is really the marriage of three techniques already in clinical practice today, bringing together robotic bronchoscopy and microwave ablation along with the advances of intraoperative CT imaging to offer patients ablative therapy using the endoluminal approach.

Now, let's take a minute and see how this all comes together. A typical room setup you can see here: the Monarch robotic bronchoscopy tower, intraoperative cone-beam CT imaging system, and the Neuwave microwave ablation system.

We begin by navigating the robotic bronchoscope to the target lesion. Once in position, the robot is locked and this provides a stable system to advance the flexible microwave ablation probe into place. The probe can be visualized at the distal tip of the robotic bronchoscope to ensure accurate positioning, which is also confirmed using intraoperative CT imaging, identical to the workflow today with percutaneous ablation.

Once the ideal position is confirmed, the ablation procedure is performed. When complete, intraoperative CT is again used to confirm complete tumor ablation and to ensure adequate margins have been achieved. And if needed, additional ablations are performed to ensure we have achieved complete tumor coverage.

The probe and the Monarch bronchoscope are then removed, and in cases where more than one lesion may be present, as you can see here, and may be the case in patients with oligometastatic lung disease, these could be treated at the same time, in a single procedure.

Of course, and as with any new therapy, it is critical to evaluate the potential benefits and risks, and I want to spend a couple minutes and review that now.

As we've discussed, there is general equipoise regarding which modality we choose to achieve local control, be it surgery, SBRT, or thermal ablation. And the decision to pick one approach or another is complex and based on multiple factors including tumor size, location, prior therapies the patient may have received, and perhaps most important, the wishes of the patient and the expertise of the caring physician. But I think it is important that we examine the benefits and risks as it relates to each of these currently available therapies.

We feel transbronchial ablation provides patients an option that has unique benefits when compared to each of them. The darker green here highlights these benefits, while the gray describes what we see as the major disadvantages.

Surgery is frequently used for local control and is, in many instances, the preferred approach. But we know that many patients are not candidates for surgery or prefer not to have surgery. And even when surgery is possible and appropriate, lung resection can result in a loss of pulmonary function and comes with significant detriment in quality of life and the recovery period.

SBRT is another invaluable tool in treating patients with oligometastatic lung tumors but requires multiple treatment sessions with frequent repeated visits to the radiation center.

And percutaneous ablation, the closest comparator to transbronchial ablation, is typically used in patients with small tumors. But the percutaneous access route is associated with a significant rate of pleural complications, namely pneumothorax, which the bronchoscopic route of delivery, we believe, is likely to reduce.

On the other hand, transbronchial thermal ablation will require general anesthesia, certainly a risk when compared to SBRT and at least in some institutions' practice of transthoracic thermal ablation.

In addition to these short-term risks and benefits, we also see longer-term benefits with this approach. Unfortunately, many patients with oligometastatic disease who undergo local therapy will develop a recurrence at some point in the future. Thermal ablative therapy has minimal impact on pulmonary function, making it a repeatable intervention to treat a localized recurrence, if it should become necessary. And it preserves the option for future surgery or radiation therapy if those modalities are felt to be the best option for the patient.

So in summary, we believe the precision of robotic-assisted transbronchial thermal ablation can provide patients with a minimally invasive, pulmonary function-sparing, single-session therapy to achieve local control that is repeatable, preserves the options for all future local therapies while also maintaining the patient's independence and quality of life.

I will now transition to my colleague, Dr. Philippe Szapary, Clinical Development Head of the Lung Cancer Initiative.

DR. SZAPARY: To quantify the benefit-risk profile of robotic-assisted TTA, we designed a clinical study under an IDE with substantial feedback from the Agency over the last 2 years and with significant input from experts in the interventional radiology, pulmonology, and thoracic surgery communities. This morning I will present the most salient features of the study to facilitate your discussion over the next 2 days. I'll focus my presentation on three key areas: study design, patient population, and endpoints.

The objective of the study is to assess the safety and effectiveness of robotic-assisted TTA in patients with OML. We considered a number of study designs to evaluate the benefit-risk profile of TTA, including both single-arm and randomized designs. Randomized controlled trials, or RCT, while the gold standard, was not deemed appropriate in this specific patient population.

When designing an RCT, there are two basic designs: superiority and non-inferiority.

In the context of this population, a superiority design would require a "no local control arm," which we do not think is an option based on current practice. The second option would be a non-inferiority trial design, which would pose two problems. Firstly, the choice of a single comparative therapy would be challenging since, in practice, this choice is highly individualized based on a number of factors such as patient preference, lesion size, and lesion location. The second issue with non-inferiority designs will be the sample size required to establish non-inferiority would not be feasible in this limited patient population.

Here are examples of RCTs in this patient population which highlight some of the challenges. For example, the pulmonary ICC study of surgical metastasectomy versus no local therapy did not enroll fully and closed prematurely. As a result, we opted for a well-designed single-arm study powered based on the performance goal derived from the systematic review of the literature. We believe this design can achieve both goals of characterizing the safety profile of the procedure, as well as its relative efficacy.

To minimize the heterogeneity of our population, we are proposing to enroll a limited number of common histologies. In addition, we plan on using accepted definitions of OML with the presence of at least one lung lesion. We will limit the trial to peripheral lesions of less than or equal to 2 cm based on literature showing better local control rates in lesions of this size. We plan to enroll patients whose primary tumor is controlled and where the intent is to treat all sites of oligometastatic disease. The primary efficacy of local control will be measured at 30 days. But in order to adequately characterize the benefit-risk profile, we plan on studying up to 145 patients with 1 year of follow-up.

Finally, given that there are strong institutional and patient preferences on how to approach the various sites of oligometastatic disease, a multidisciplinary team of providers at the site will assess the suitability of inclusion in the trial.

The primary endpoint of this study will be technique efficacy, also known as TE,

which we believe is an appropriate surrogate for local control. TE is measured using CT imaging and is defined by an ablation zone that clearly overlaps and encompasses the target tumor, as shown on the images on this slide. This will be measured objectively and rigorously by an independent review committee with pre-specified success criteria. TE is also the current standard used in clinical practice and recommended in guidelines when evaluating the effects of percutaneous ablation.

The 30-day time point is important because it coincides with when typical follow-up CT scans are done in clinical practice and coincides with our primary periprocedural safety analysis. Finally, it's the time before which most systemic medications may be started, thereby limiting any potential confounding.

While TE is a short-term technical endpoint, we believe that in the context of thermal ablation it could be considered a surrogate for other clinically relevant endpoints. To illustrate this point, we conducted a systematic review of the literature and meta-analysis of thermal ablation modalities, both RFA and microwave. While a limited number of studies exist in OML patients with some patient heterogeneity, this graph on the right shows that directionally, TE is correlated with local tumor progression over 2 to 3 years. Based on these data, we believe that 30-day TE is an appropriate measure to determine local control in the OML population and therefore can be considered as the primary endpoint of the study.

Safety is a critical endpoint to assess for a new technology and will be assessed throughout the study and monitored by an external data safety monitoring board with a focus on the adverse events listed here occurring in the 30-day periprocedural period. Beyond short-term endpoints, we will assess the oncologic endpoints listed here over 1 year. All endpoints will be assessed based on imaging using an independent imaging review panel applying pre-specified success criteria. To capture important patient-related

outcomes, health-related quality of life will be measured using validated oncologic questionnaires. Finally, preservation of lung function will be measured longitudinally using PFTs.

In summary, we believe OML, while uncommon, is a clinically important manifestation of malignancy and one that has significant impact on patients.

Local control of OML, regardless of the modality chosen, has the potential to extend life. Surgery, SBRT, or percutaneous thermal ablation can achieve local control in this patient population.

We are proposing to study robotically assisted transbronchial thermal ablation as a new access method for delivery of thermal energy. We believe that by combining the precision of robotics with microwave ablation, that this approach can provide a minimally invasive, repeatable procedure with a favorable benefit-risk profile relative to other available therapies.

We hold that in this population specifically, well-designed, single-arm studies of TTA using short-term endpoints supported by longer-term follow-up can adequately characterize the benefit-risk of this approach.

On behalf of Johnson & Johnson, I'd like to thank you for the opportunity to present to the panel today.

DR. BLAKELY: Thank you again to everyone who has participated.

This is Brandon Blakely from CDRH and this now concludes the first portion of this virtual workshop. We will now break for lunch and we will reconvene at 1:30. Thank you all.

(Whereupon, at 12:56 p.m. a lunch recess was taken.)

AFTERNOON SESSION

(1:30 p.m.)

DR. BLAKELY: Hello, everyone. I'm Brandon Blakely from CDRH and it is my pleasure to introduce our first session, an overview of oligometastasis to the lung, or OML. Our session will begin with two amazing speakers, Dr. Anthony Conley from MD Anderson Cancer Center and Dr. Puneeth Iyengar from UT Southwestern Medical Center. We will then hold a panel discussion on the parameters defining OML moderated by Dr. Michael Offin from Memorial Sloan Kettering. Thank you.

DR. CONLEY: Hi, I'm Anthony Conley, an associate professor in the Department of Sarcoma Medical Oncology at MD Anderson Cancer Center and I'll now begin my talk.

All right. Okay, so here are my disclosures for this particular talk. I'd like to think of this as an overview to the session from the perspective of a medical oncologist, so I'll briefly discuss metastasis and oligometastasis and some minor differences, as well as the clinical and biological characteristics of oligometastasis. I'll also briefly touch on oligometastatic-directed treatment, though clearly the details will be much more involved with some of the other speakers that we've already seen today and hopefully throughout the session, as well as some brief future considerations followed by my conclusion.

So starting with metastasis, of course, when we think of metastatic disease, I tend to think of it as dissemination of cancer cells through a primary tumor to other sites of the body. Now, that's a rather simplistic view of the situation, but at least it illustrates sort of the key point that the disease has the ability to move to other sites of the body and potentially impart harm. We know that metastatic disease is rarely curable and that it is the leading cause of cancer-related death among cancer patients.

In general, most medical oncologists will treat metastatic disease using systemic agents such as cytotoxic chemotherapy. Although I'm a medical oncologist focused with

sarcoma management, for the purpose of this talk, I'll focus more on the most common subset, the non-small cell lung carcinoma patients.

If we look at metastatic non-small cell lung carcinoma, you know, in the past this was treated with doublet chemotherapy which was associated with inferior response rates and survival metrics compared to many of the modalities available today. With the advent of genomic technology in the clinical arena, of course, we can now mark patients with specific alterations and then tailor their treatment and this has yielded, of course, much better response rates and improved overall survival. Even more recently with the addition of immuno-oncology drugs such as pembrolizumab, we are seeing improvements even for patients that do not have some of these selected genomic alterations.

You know, in terms of metastasis, it is definitely a hallmark, and perhaps one of the essential ones, considering that many of these other processes that we normally think about can actually occur in benign tumors that don't metastasize. So in this sense, invasion of metastasis, in my opinion, represents one of the most important hallmarks for cancer development.

As a medical oncologist, I think of treatment from two broad categories. First and foremost, for the reduction of disease-related signs and symptoms, I think of this in terms of tumor-related pain; hemorrhage, which can occur in the lungs or any other site of the body; airway obstruction; bowel obstruction; and for those patients that have PNS involvement, urologic deficits that can certainly impact their quality of life. And of course, and more importantly, in the long term I think about whether or not I can improve a patient's survival with the modalities that I use or that I request assistance with from other consultants.

But clearly, there's a difference in terms of how we think about metastatic disease. On the left, I have a patient with an extraskeletal myxoid chondrosarcoma, a rare variant

that typically has very widespread pulmonary metastatic disease, followed by the patient on the right, which is also a type of chondrosarcoma called conventional chondrosarcoma, in which case this is a Stage IV patient with clearly very limited disease compared to the other person. And as you can imagine, the types of modalities needed to control the disease process in both of these patients may be unique, different, and be different in terms of quality of life and survival metrics.

So in terms of oligometastasis, if I think back to when some of this first occurred, in the 1890s Dr. Halsted, a surgeon, proposed a contiguous cancer model using breast cancer with the idea that tumors begin at the primary site, directly extend to regional lymph nodes, and then disseminate to distant organs, and thus treating the tumor at an early point of time would render the patient most likely to survive their illness.

Over the next 60 years, this definition then evolved to include a systemic cancer model where the other thought was well, if it's apparent clinically then it's likely already metastasized.

By the 1960s, Dr. Rubin wrote an editorial in *JAMA* where he actually discussed the possibility of curing select metastatic patients based on the clinical characteristics of the disease and interestingly enough, even proposed a remarkable immunological theory regarding how this likely takes place.

By the 1980s, clinicians were now utilizing modalities such as radiation and surgery for the treatment of select metastatic patients.

But it was in the 1990s that Drs. Hellman and Weichselbaum coined the term oligometastasis and brings us to the present where we think of oligometastasis as a spectrum of possibilities generally limited by the number of metastatic sites and to the extent a disease is amenable by metastasis-directed therapies such as radiation, surgery, or ablative technique.

So when I think about treating a patient with oligometastatic disease, I am still thinking about how can I reduce their disease related symptoms if they, in fact, have disease related symptoms in the oligometastatic setting, and also think about improving survival, if I can.

But then there are also other factors, as well. Take the elderly patient that may not tolerate some of the cytotoxic chemotherapies we give. Or take, for instance, patients that have Li-Fraumeni syndrome or retinoblastoma that are exquisitely sensitive to radiation techniques and the increased risk of secondary malignancy, how should I go about treating them? Should I position them to be seen by a thoracic surgeon or in this case, a pulmonologist that could potentially provide them another option that would lower their potential risk from the treatment itself?

And there are also biological factors that we need to think about in the long term with some of the select points that I'll bring up. And with this, I'll go over the clinical and biological characteristics.

So in general, I think most people that treat cancer realize that there has been organotropism that takes place with cancer, meaning that tumors tend to migrate to other parts of the body that are not necessarily the same amongst all malignancies.

Among the 400 types of malignancies that exist, many of our basilar-based (ph.) cancers arising from the GI tract have a tendency to either move to the liver or the lung. Kidney cancers can prefer lung metastasis, bladder cancers, the lung, and even though my specialty is not represented in this particular slide, soft tissue sarcomas and osteosarcomas also have a high predilection for lung involvement. But even though lung cancer itself may have a predilection for other sites, they still represent the most common fraction of patients with oligometastatic disease and thus it represents an important area of interest for the medical oncologist managing this disease.

If I think about the biological differences using non-small cell lung carcinoma as an example, Rashdan et al. looked at some of the basic variables from a clinical standpoint looking at growth potential, impact to the primary tumor, looking at cancer cell migration and distant host sites, what you'll see is that there should be intrinsic differences between oligometastatic disease and systemic metastatic cancer.

And what's been gleaned from prior studies of patients that have successfully had improved outcomes to consolidated and local therapy is that they typically have less metastatic disease, they typically have qualitative differences in the site of metastasis such as the absence of lymph node and bone involvement, nonclinical pathology. These are typically patients that develop recurrent metastatic disease rather than metastasis at the primary diagnosis, they typically have smaller primary tumors, and they're generally younger patients, which also alludes to the biological differences from a genomic standpoint, as we know that nonsmoking related non-small cell lung carcinomas are associated with specific genomic alterations compared to the individuals of an older age that have tobacco exposure.

And with that said, we can see that in non-small cell lung carcinoma there have been a number of different parameters looked at, not simply just genomic, but looking at the new microenvironment, looking at epigenetic changes, and clearly showing how there's a progression of events from the cell lesion extracellular matrix and essentially providing through the bloodstream and eventually setting up shop in the distant organs where it then becomes clinically apparent to imaging and to the patient.

If I look at colorectal cancer as another example, this is a successful study looking at oligometastasis involving the liver. The authors of this paper were successfully able to develop a risk stratification schema based not only on clinical characteristics but more importantly on genomic alteration using and confirming their data with a public database of

genomic information with clinical variables, and what you can see here is that they have a conical (ph.), an immune and a stromal subtype each associated with different frequencies but also associated with unique molecular signatures amongst each type with the ability to impart either a favorable prognosis or an unfavorable prognosis. This is important when we think about developing trials for oligometastatic patients, in some cases specific to histology.

In summarizing some of these determinants, looking at predictors of oligometastatic disease, there's been a number of different areas of investigation for a wide variety of tumors including the use of microRNA, looking at lots of specific genes such as Matt Horlock, as well as through the usual clinical correlates such as size, location, disease-free intervals of extended periods of time. Needless to say, all of these factors together makes the selection of treatment for oligometastatic disease a lot more interesting and hopefully fruitful for the patient undergoing these therapies.

So if I think in general about oligometastatic directed treatment, there are certain things that the clinician or the medical oncologist generally think about, histology dependent variables such as, for instance, renal cell carcinoma, melanoma, sarcoma being diseases where oligometastatic treatment may make sense given that there are variable rates of disease amongst these different histologies, looking at the individual metastatic characteristics such as the number, most trials look at one to five lesion as a definition for oligometastatic disease; looking at the size of the lesions, obviously if these are too large, they may not be amenable to certain techniques; and also qualitative factors such as the location of the tumor in proximity to the great vessel or other areas that might make it substantially more difficult for a technical procedure.

There's also synchronous and metachronous disease, the timing. In other words, in most studies amongst different histologies, we tend to see that metachronous disease is

associated with a better outcome than synchronous, though this hasn't been validated in all tumor types in a systematic manner.

Then there are also newer concepts such as developing oligorecurrence, oligoprogression; in other words, patients responding to therapy but then having progression, how do we treat them?

And then as I mentioned earlier, age, patients with contraindications to specific types of metastatic directed therapies, and hopefully in the future, omic or biologic determinants that might help us with better selection.

But how is this relevant to the medical oncologist? Well, one German study evaluating patients presented to the tumor board found that at least one-fourth of all of their patients with metastatic disease had oligometastatic presentation and it is such a value having a group to help assist with planning of the treatment of these patients. And so this can vary depending on whether the clinicians are in an organ-based setup or whether they are general oncologists treating any patient that walks in the door.

And of course, when a medical oncologist is speaking about who to refer the patient to, there's clearly a number of possibilities now, including the gold standard of surgery or radiation and more recently, the application of image-guided ablative therapy through our interventional radiologists, and even more recently, bronchoscopic techniques that our interventional pulmonologists are now able to do and hope to utilize these new techniques.

And so these are all things that we think about carefully. From a medical oncology standpoint, I think this is where it's really important to have a tumor board to help provide insight and guidance for these particular areas.

And fortunately, there are even Phase II randomized studies that have now been published demonstrating, at least in smaller sample sizes, that there are potential benefits in terms of progression-free endpoints and, as someone alluded to in an earlier

presentation, the ability to free the patient from needing specific therapies that, which as a medical oncologist, unfortunately, chemotherapies can be rough. Even immunotherapies, which are generally considered to be much safer, are not free of all adverse events. And so having metrics like perhaps treatment-related free survival would be an interesting endpoint for some of these disease trials that are being under consideration.

And importantly, here are these two models that were presented in the *Journal of Oncology Practice* several years ago where the authors were looking at the number of metastases, regional lymph node and regional lymph node involvement, and presence of metastasis by imaging as ways to guide when a patient should consider local consolidated therapy versus systemic therapy first, or in patients that have widely metastatic disease but develop a substantial benefit from their targeted therapy and are now reduced to a very small number of residual pulmonary lesions, which are the patients which would benefit from local consolidated therapy.

And finally, from a clinical trial structure, obviously there are other folks in the industry that have done a fantastic job illustrating some of these finer details in other presentations, I'll just make it a point that it doesn't really have to be substantially difficult in terms of randomizing standard of care to standard of care plus oligometastatic-derived treatment or even consideration of things like I-SPY designs where multiple modalities are considered.

Clearly, eligibility criteria and endpoints need to be carefully managed as we think about how to develop the appropriate trials for either all histologies or specific histologies like non-small cell lung carcinoma or certain sarcomas among other malignancies.

And then finally, we should take advantage of trying to understand the biology better as we run these clinical trials; in other words, building in time points where we collect data from blood, from tumor tissue, before and/or after treatment and also follow

them on a longitudinal protocol so we can better understand the natural disease history of these patients, especially in an era where there are so many modalities present.

And with that, I'll just conclude that obviously the definition for oligometastatic disease is evolving and will likely depend on our technologies.

Biology is quite unique and interesting and may help us in determining better ways of treating oligometastatic disease.

But most importantly, there's definitely much more work that is needed to understand the biology and to improve the outcomes for patients with oligometastatic disease. Thank you.

DR. IYENGAR: Hi, my name is Puneeth Iyengar and I'm a thoracic radiation oncologist at UT Southwestern Medical Center. Today I will be providing definitions and optimal management of oligometastatic disease through the lung from a radiation oncology perspective.

These are my disclosures.

I wanted to provide a case presentation, so basically a 65-year-old male presenting with a right upper lobe mass and mediastinal lymphadenopathy. A PET/CT shows that he had disease in his right upper lobe mass, multi-station N2 disease in the left adrenal. MRI of the brain shows isolated brain mass, and a biopsy of the disease, it shows adenocarcinoma of the lung. For this Stage IV non-small cell lung cancer, which should be the disposition, if anything, for a radiation oncologist.

These are the treatment options, whether it's systemic therapy alone, radiation to the brain followed by systemic therapy, radiation to the brain, radiation to the adrenal, and then systemic therapy, radiation of the brain, radiation to adrenal, and chemo-radiation, radiation of the brain and then systemic therapy alone followed by consideration of consolidated radiotherapy.

We chose to SRS the treatment of the brain metastasis, provide first-line systemic therapy consisting of carbo/pem/pem, reimage the patient, enroll the patient on NRG-LU002 and for which the patient was randomized to the local consolidative therapy arm. We treated the intrathoracic primary disease and the adrenal metastasis with SBRT, and then we continued the patient on systemic therapy.

But eventually, what we really do note is that biology effectuates outcomes, especially in the cases and the discussions that I will have with respect to non-small cell lung cancer metastases. And one of the real questions is now, is limited versus widely metastatic disease another thing that we need to take into account? So with better systemic therapy comes the notion that we may need to employ local therapy to continue to improve the therapeutic ratio.

What is the rationale for local treatment for metastases? The development of widespread availability of modern systemic therapies would potentially demonstrate a role for local therapy. The idea that systemic therapies are not perfect and cannot stand alone, the imaging tools that now can detect earlier evidence of metastatic disease, and the idea that we could perhaps turn metastatic cancers into a chronic illness and potentially even a curable illness and so therefore, combination therapies are very important.

The notion of oligometastatic or limited metastatic disease has really evolved from the days of the initial discussion by Hellman and Weichselbaum in the 1990s, where they describe the evolution of metastatic capacity to potentially have an intermediate state in which spread may be limited to specific organs and metastases might be present in limited numbers. Hence, the idea of oligometastases.

This is a diagram that suggests the spectrum from localized disease that would be predominantly treated with surgery and radiation and local therapies to oligometastatic disease where the disease has spread from a few sites in the body and you may want to use

the combined modalities of systemic therapy and local therapy, and ultimately widely metastatic disease where the focus would be primarily use of systemic therapies.

We should also think about oligometastatic disease in terms of timing. Oligometastatic disease can be present at the timing of primary disease diagnosis, i.e. synchronous disease. Oligometastatic or oligoprogressive disease can also be present sometime after the primary disease has been treated for earlier stage disease, i.e. in the metachronous metastatic setting.

So continued rationale for these local therapies in metastatic disease. What I have highlighted in red here suggests the fact that most sites of recurrence or progression of disease in the metastatic setting occur in original sites of gross disease. This is relevant in the setting of systemic therapies including cytotoxic chemotherapy and in the modern era of immunotherapy. So if original sites of gross disease are the most persistent to recur, why not consider local therapy to reduce that likelihood?

The other data that we have supporting the use of local therapy, of course, comes from our surgical oncology colleagues who have been using it for sarcoma and colorectal cancer to good result, especially when they've had limited metastases to the liver, lung, or brain. And survival has actually been demonstrated in some of these scenarios.

So along with the idea of oligometastatic disease came the advent and development of stereotactic body radiation therapy and this idea, SBRT, also known as stereotactic ablative radiotherapy, is a concept of using very high doses of radiation to limited areas of disease with few fractions with image guidance. And the reason that this is ideal for oligometastatic disease is there are few sites of limited metastatic disease amenable to SBRT noninvasive treatments with no complications from surgery, side effects, or post-op recovery and the idea would be that SBRT would go hand in hand with systemic therapies in managing oligometastatic disease. The other advantage is SBRT is done in a very quick

manner, allowing the patients to continue a return to systemic therapy in a rapid fashion.

Over the initial decades of the use of SBRT and the idea of oligometastatic disease came to fruition, we saw many studies that suggested that local therapies in the form of SBRT to oligometastatic sites of disease in multiple disease locations could potentially be beneficial to the patients, and certainly safe and feasible for the patients.

So I'd like to talk about the use of local therapy for oligometastatic disease, especially in the setting of lung cancer, as a treatment paradigm and as a disease paradigm in three settings: consolidation, oligoprogression, and I really won't focus on abscopal effects because there's limited data to support that.

These are the main completed studies in a randomized and prospective fashion that have been completed for oligometastatic disease and use of local therapies in non-small cell lung cancer. The reason I prioritize non-small cell lung cancer aside from the fact that I treat and study metastatic non-small cell lung cancer and local therapy is the fact that the thoracic field has really pushed the envelope in trying to understand and use randomized trials to support the use of local therapies in the management of oligometastatic disease.

The MD Anderson study, of course, is a landmark study by Gomez and colleagues. It demonstrated that in a consolidative approach, treatment with local therapies for synchronous or metachronous oligometastatic disease from a primary non-small cell lung cancer was safe, feasible, and not only improved progression-free survival threefold, but also had a significant overall survival benefit.

Our colleagues north of the border, as well as in Europe, also did a study where they looked at oligometastatic disease from multiple different primary cancers and what they showed was that, again, local consolidative therapy improved progression-free survival and overall survival. But this was a study that was only looking for a signal for benefit, so their Alpha and Beta ratios were leveled at 0.20. Again, they were looking for really a treatment.

On the other note, three out of 66 patients died from treatment-related deaths, at least that was what the attributions were, and so we need to think about toxicities as we consider treatment of oligometastatic disease with any form of local therapy.

These two studies were extremely important, but there was significant heterogeneity in these patient populations and ultimately, these studies were done prior to the more modern era of needle therapy as the systemic therapy of choice. Our group at UT Southwestern Medical Center did another study where we prioritized only the use of radiation in the form of SBRT as a local therapy. We tried to limit heterogeneity by including only patients that were not known to have disease with targetable mutations, and we also insisted that all patients received maintenance systemic therapy after their local radiation therapy. And in this randomized study we also saw a tripling of PFS with the use of local therapy similar to the Gomez et al. study. What we also found was that patterns of failure were changed, no longer were the first sites of disease the first sites of failure, patients had delayed and distant patterns of metastatic spread.

But with better systemic therapies in the form of immunotherapy, the real question is, in this modern era, will local therapies synergize with systemic therapies in the form of immunotherapy to optimize outcomes or will the immunotherapies, in fact, dilute the benefits that local therapies offer, at least in the setting of non-small cell lung cancer since the immunotherapies have gotten to be better and better in terms of their PFS and OS benefits?

And this is just another slide showing some of the more recent immunotherapy trials being combined with radiation to see if there is a synergy.

And so this brings us to the accruing Phase III trials that are trying to answer the question of the benefits of local therapy in the form of radiation in the management of oligometastatic non-small cell lung cancer. I'm the lead of NRG-LU002, which is, at this

stage, arguably the largest randomized study looking at local therapy in the management of oligometastatic disease. We've enrolled 218 out of 378 patients over 70 sites that have enrolled patients. The Phase II has been completed and we're trying to generate a readout to determine whether PFS benefits are enough to move the study to the randomized Phase III portion of the trial. But again, the general framework of the study is that patients with oligometastatic disease who receive induction are then consolidated with no local therapy or local therapy and then they go on to continue to receive maintenance systemic therapy in both arms and overall survival hopefully will be the main primary endpoint. And it has truly become an IO minus/plus radiation trial because more than 80% of the patients on the study are receiving IO-based systemic therapy.

SARON is another study from our UK colleagues looking to see the same benefits of consolidated therapy. Unfortunately, due to enrollment issues, they've only gone down from a Phase III study to a Phase II study; that will be supportive of other studies with respect to treatment decision making.

So if we look at the next scenario, not consolidation, and we know consolidation means treating patients after they receive some systemic therapy to ensure that they truly have oligometastatic disease, giving them local therapy at that time, and then moving on with subsequent systemic therapy. Oligoprogression indication is to really use local therapy only when the patients have progression of disease after receiving their initial first-line systemic therapy.

And we published a single-arm Phase II study that demonstrated a very significant PFS of 14.7 months and an OS of 24.4 months. And even though this study is of 24 patients, and it was done in collaboration with the University of Colorado, this study was important because it suggested that the paradigm of using local therapy in oligoprogressive disease may actually be beneficial for this patient population. And again, the patterns of failure

switched from being primarily a local failure pattern up front to being a distant failure as first site of progression.

And now, more randomized studies are maturing and we'll get a better sense of whether local therapy at oligoprogression will be another treatment paradigm that may show benefits with respect to PFS and OS.

Interestingly, one of our colleagues from Memorial Sloan Kettering, Jillian Tsai, presented her data looking at randomizing patients with non-small cell lung cancer and breast cancer with oligoprogressive disease to local therapy and not local therapy, the PFS benefit was obvious with non-small cell lung cancer but not breast cancer. So this suggests that oligometastatic disease from different primary cancers may have different outcomes based on the local therapy approaches.

But ultimately, local therapy should not be standard for oligometastatic disease and we really should continue to treat these patients on protocol or if there is no protocol or trial at your institution, as part of a multidisciplinary decision-making process. And the reasons are we still don't know how to really define oligometastatic disease. Is it three mets versus five mets? Is the number even relevant? Most studies at this stage have prioritized three to five mets.

Does the location of disease in metastatic disease matter? Yes. Patients with liver metastatic disease may have worse prognoses than patients with bone or lung.

Does the volume or size of mets matter? Probably not, because we can adjust our SBRT doses to manage any volume of disease.

Should patients with N1 or N2 disease be included? Yes, because we need to treat the primary disease and that's what most of the studies have shown.

And is histology relevant? Yes, because we need to understand the natural history of disease in the setting of presence or absence of systemic therapies to incorporate ideal

local therapy approaches and that's why sequencing and whether the oligometastatic disease is from CRC versus RCC versus non-small cell are all very relevant.

Do we really know the optimal sequencing of treatment? I try to provide evidence, at least for non-small cell lung cancer, that consolidation in oligoprogression may be the sweet spots.

What is the right overall metric to assess local therapy benefits? I think, to appease all of the multidisciplinary teams, it would be appropriate to show that local therapies benefit overall survival, but we should look at all in multiple metrics.

And ultimately, we need to finish these larger Phase II/III studies before we can really start adjudicating whether the local therapies, especially in the form of radiation, offer true benefits without significant toxicity for our patient populations.

And why is this all important? It's all important because SBRT practice pattern studies suggest that a predominant proportion of radiation oncologists will use SBRT whether on or off trial for the management of oligometastatic disease.

So oligometastatic disease is relevant potentially to all primary cancers and must be discussed with respect to whole body distribution, only then can one identify whether a local therapy is necessary, sufficient, and/or beneficial. It is with this understanding, along with the idea that the larger Phase III studies for use of local therapies have not been completed, that we should think about the fact that local therapies, including radiation, should be used only after multidisciplinary discussions.

And at the end of the day, oligometastatic disease to the lung is but one of many locations that this spectrum of disease may land, requiring a close examination of the entirety before making a judgment on the uses and benefits of local therapy.

Final thoughts. Complete enrollment on studies is key, but we need to get more than simply the endpoints, we need to learn more and that includes learning about

sequencing, readouts, biomarkers for predicting which patients will benefit from local therapies or which patients will met out to large areas of anatomic sites within a short period of time, and we need to understand the type of optimal systemic therapy with XRT.

Biologically, I think the most interesting aspect will be for us to appreciate how the evolution of cancer metastases exist and/or clonal evolution along with resistance mechanisms with more biological insight gained from these clinical trials of oligometastatic disease. Thank you very much.

DR. BLAKELY: Thank you again to Dr. Conley and Dr. Iyengar for the great presentations.

We're now going to transition to our first panel discussion regarding the parameters defining OML, which will be moderated by Dr. Michael Offin from Memorial Sloan Kettering. I will now hand it over to Dr. Offin.

DR. OFFIN: Thank you, all. So good afternoon, my name is Michael Offin. I'm a thoracic medical oncologist based out of Sloan Kettering in New York. Firstly, I want to thank you all for attending the talk today and to the FDA for inviting me to moderate.

So this 60-minute session is comprised of four distinct questions focused on the definition of oligometastases to the lung. Next slide.

This will be comprised of eight panelists: two medical oncologists, Dr. Conley and Dr. Camidge; two thoracic surgeons, Drs. Harpole and Vallieres; two radiation oncologists, Drs. Iyengar and Kavanagh. And we will also have two members of the FDA joining us, Drs. Blakely and Drezner, to specifically answer regulatory and FDA questions that might come up during the discussion. Next slide.

These are my disclosures. Next slide.

With that, I think we should dedicate our time to the discussion. Next slide.

So the first question I pose to the panel: What is maximum number of lung nodules

appropriate for the classification of OML? And how are other metastatic sites factored into this population?

Dr. Harpole, if you want to start us off?

DR. HARPOLE: A good question. I guess the first thing that we've heard from multiple of these excellent reviews that we heard from all the modalities, as well as the sort of position guidelines from each of the societies is, right now I think we're going to define this as limited to the lung because obviously oligometastatic disease can have multiple locations. In fact, the NRG trial that we designed about 6 years ago when I was the head of the thoracic malignancy steering committee, we limited it to five sites but they weren't all confined to lung. And so I think that certainly five or less is a reasonable number and I think three may be more of a medium if we're looking at lung nodules because I think we're trying to look at efficacy.

My concern is that when patients have more, five or more, we very well may be at the boundaries of oligometastatic disease and if we're trying to look at efficacy of these local therapies, we don't want this to be clouded with metastatic disease and poor outcome of patients. So I mean to truly define this, I would certainly say for these initial studies, I might be a little more conservative and do three, one to three, and we'll hear what the other panelists have to say.

DR. OFFIN: Thank you. Dr. Conley, do you have a comment?

DR. CONLEY: Yeah, I agree with Dr. Harpole. I think that the definition sort of wavers or changes over time, the numbers may increase. I think for the purpose of keeping trials not simplistic, but easier to manage, I do think that maybe having a number like three is reasonable, maybe five in some circumstances.

You may also have to think about which pathology you're choosing for this, presumably, and I understand that most of this will likely be done in primary lung cancers,

but as a sarcoma specialist, I can tell you that we go to our consultants all the time for treatment of oligometastatic disease because frequently our patients will have a limited number of metastases and knowing what the optimal time point is, let's refer them and include them for these modalities in the chain over time.

But yes, in general, I do think that three to five is very reasonable in terms of organ involvement. I think that also probably is histology dependent, right, colorectal with liver and lung. You know, certainly, like I said in my space, we can have a lot of soft tissue metastases as well as lung metastasis and so, those are areas that -- well, the soft tissues past the areas where patients can benefit from a treatment standpoint or a clinical standpoint, they have pain, sometimes less motion or range of motion issue, but you certainly be must more complex when you're looking at other organs such as the liver and such. But yeah, I would say three to five would be what I would limit it to.

And I guess some studies have been introduced where you can have a maximum of three different organs involved, I honestly think that really just depends on the circumstance. I think within the scope of pulmonary disease, obviously you think about whether or not you want to have other sites.

I do think that it's important to consider other metrics, I think survival is a wonderful metric, but as we get better and better with marking a target, I think it's going to be much more difficult to determine.

And for the patient, yes, they want to survive longer, they're thinking more about immediate things. So even looking at possibilities like treatment-free related situations may be relevant. Maybe not so for a ROS1 effusion-driven lung cancer patient but, for instance, for a prostate cancer patient on antigen deprivation therapy, it may be appropriate to give them time off, if it's possible, and even for lung -- for our plume (ph.) patients where we typically use conventional cytotoxic chemotherapy, having a break of even a month is

valuable to some patients and so defining those variables, I think, is important, but it's clearly dependent on histology.

DR. OFFIN: Yeah, very valid points, I mean -- I'm sorry.

DR. IYENGAR: Yeah, I echo what Drs. Harpole and Conley stated. So when we talk about maximum number of nodules in a given organ, I think three or fewer is probably the most, at least, appropriate to thought process as of now and that is what's been integrated into the studies that Dr. Harpole championed through NRG, of course, and that Dr. Conley has discussed.

I think that the second part of your question is really apropos, which is how are other metastatic sites factored into this calculation? And so that's kind of what a multiple number of us have tried to explore is the idea that more than likely we shouldn't look at oligometastatic to the lung as an isolated process but to look at it globally and if we have seven other sites of metastatic disease extra-thoracically, it really doesn't matter how many lesions are in the lung, one would make the argument that that's a polymetastatic disease process.

And so I think every time we think about oligometastatic to the lung, we have to factor in what's going on beyond the thorax, but I think if we are just focusing on specific organ entities such as the lung, which we are here, I would say anything more than three lesions, three to five, would probably present a polymetastatic disease process that local therapies may or may not be helpful for.

DR. OFFIN: Very good. I'll kind of open this to the floor now to see if there are other comments or otherwise I can kind of stop here.

DR. KAVANAGH: I'll just add, for completeness, there is an ongoing study, the SABR-COMET 10 study, and maybe that will be a little bit informative in this regard, but it's David Palma's follow-up study to the one that Dr. Iyengar mentioned and it includes patients with

4 to 10 metastatic lesions, so we anxiously await those results to see if they inform selection down the road.

DR. CAMIDGE: And I'd like to throw --

DR. OFFIN: One of the -- I'm sorry.

DR. CAMIDGE: Go ahead, Mike.

DR. OFFIN: Well, no, I was going to suggest a topic.

DR. CAMIDGE: So one thing I was going to throw out, given that we -- you know, we have such great radiation oncologists on this call, is to recognize that when we're dealing with thoracic, a thoracic primary, you guys tend to treat the mediastinum as one site even if there are 57 lymph nodes involved and so -- which I'm totally on board with, I just want to not give ourselves a definition that someone not appreciating the subtleties of radiation oncology might trip over.

DR. OFFIN: Dr. Iyengar, do you want to say something to that or --

DR. IYENGAR: I totally agree with Dr. Camidge. You folks at the University of Colorado really have been part of the spearheading of all of these approaches and so you're absolutely right, we do group multi-station N2 disease with single-station disease and what we do know for sure, though, is -- I wouldn't say for sure, but what we do hypothesize is that treating primary disease is equally important to treating the metastatic sites. If we want to develop significant progression-free survival intervals, that may translate into an overall survival benefit. So we will have to understand how to optimize local therapies for larger, Stage III-like primary distributions in the setting of all of these oligometastatic discussions.

DR. HARPOLE: You know, I think we need to roll the clock back, back to the '70s and '80s when this work was done at Mayo, for a moment. I really do believe that we've got several questions here.

Number one, I think that we've got to make sure that the primary is gone or controlled or whatever if we're going to look at oligometastatic disease, I mean, that's got to be a for-sure. I'm wondering if we shouldn't opt in for an interval of time between control of the primary presentation of these mets or where they're handled because lots of data have shown that someone who has nearly synchronous appearance of oligo disease with the primary, they tend to not do well and I don't want those type of patients somewhat diluting the effect that may actually be important for those who have true oligometastatic disease.

So I think these are some of the things. And I also agree that limiting it to certain histologies comes to mind, like melanoma and things one might leave out, you know, colorectal sarcoma, things like that. And even in multiple lung we could all go with what would be things -- I mean, I just don't want to frontload the trial with things that are actually going to make it not feasible or not successful.

DR. VALLIERES: Yeah, if I may. This is Vallieres in Seattle, here. Hey, David. I think we're going to answer some of those questions down the road, talking about histology and so on, and I think the number has to be a little different depending on the primary. I agree that the primary has to be controlled or controllable, it's an old principle that hasn't changed.

To Ross's comment about nodal mediastinum, I think it's different whether it's a colorectal primary or whether it's a lung primary, so I think that's going to have to be discussed, as well. I think the histology matters. This question is about number. I think more than five, no. Three to five is reasonable. And we'll go into the intricacies of where the primary was, are there targeted therapies available for this particular cancer, that's what matters. And also the nodal metastases will matter depending on what the primary was. A colorectal cancer with metastatic disease to the mediastinum, that to me is out of

the box. Lung cancer isn't. Renal cancer isn't. It matters. So from the data that we have, I think we're going to have to weigh those in. I'll stop there.

DR. OFFIN: Very good. I think for time, we can move on to Question 2. Next slide.

So for the second question: Are all tissue histologies potentially encompassed within this definition of OML? Is the definition modified by specific histology? And I would add to that, how would you interplay prognostic or predictive markers in non-small cell or otherwise in that determination?

So I think to start, we had asked Dr. Camidge for comments.

DR. CAMIDGE: I think histology does matter. I think we are aware, even if we look within lung cancer, that the -- if you look at surgically resectable Stage I non-small cell lung cancer and small-cell lung cancer, they have dramatically different 5-year survival and so the sort of hidden metastatic potential can clearly vary, and I think Puneeth had also sort of shown a hint of a study where it looked more promising in lung cancer than it did in breast cancer. So part of it is to do with the underlying metastatic potential.

The other thing is to do with the drugs that we have for controlling systemic disease and so if you had a non-small cell lung cancer which had no driver oncogenes and no chance of responding to immunotherapy, I would be very skeptical that we would have a long time before the next sites of disease turn up, whereas if we had -- you know, as Michael said, a ROS1 positive lung cancer who's got a median PFS of 21 months, then I think I'd be much more optimistic. So I think it does, it does matter.

I think when we're thinking about lung cancer, the thoracic oncologists here probably need to invert our thinking. So the way we would think about this is what happens if you have like a solitary met in the adrenal whereas I think, for the sarcoma doctors, it's much easier to think of them as the lungs, there's just a solitary blob there, whereas we -- as David mentioned, we've always got to consider the primary when we have

a lung cancer.

DR. KAVANAGH: Yeah, so continuing on this line of conversation, it's a good question. I think histology certainly has to be considered. It's interesting, you know, I think on one of the slides Dr. Conley showed the URTC study, I believe, which showed that aggressive treatment of liver resection of colorectal cancer was eventually a beneficial thing, although there's a study that I don't think we've shown on any of the slides, though, I think it's the PROMIX study where there was a pulmonary resection of colorectal cancer that did not show benefit and that was explained away as a surprisingly favorable survivorship in the patients who were in the control arm. Go figure.

So be that as it may, because it's all in the past because there's a lot more genetic information that's available nowadays and so that adds just another layer of complexity, as Ross mentioned, it's a different consideration for someone who's got an oncogene-driven tumor versus not. He already mentioned the CURB study which was genetic sizing, that showed differences in oligoprogressive disease, breast versus lung. There was a slide that Steve Chmura showed at a meeting recently and I will try to describe it qualitatively, but I wish I had a visual, I don't have it.

It's his slide, I can't really show it in good faith, but what he was postulating is that there's probably a sweet spot for demonstrating the benefit of local ablative therapy to oligometastatic disease that is the place between where systemic therapy is of virtually no value and the patient is going to have a bad disease course almost no matter what, and systemic therapy is so wonderful that systemic therapy might just barely be icing on the cake. And so it's in this in-between place where the systemic therapy still needs some help and so I think whatever the histology, it's the patient population within that histology where we expect a pretty good result but where it would be good to do better and I know that's a very hand-wavy qualitative way to say it, but I think that's the sweet spot where this

combination treatment works well.

DR. CONLEY: I think there are situations where it may also depend on companion diagnostics, like I mentioned that colorectal study that developed a risk stratification, it would be great to see future studies incorporate or validate these types of systems to determine if there might be -- like you said, instead of resecting a patient that may not need resecting of their pulmonary lesion in colorectal cancer, maybe there is a patient that you determine, based on their biology, is likely to have -- and determine if you improve the outcomes in that area. And I think all too often we see lots of really wonderful preclinical data or data reviewing omics from whether it's the HPRD database or others, but then it's like where's that point to seeing it actually commercialized or become something that we can actually apply in clinical practice.

And so while we're thinking about the size of the tumor, the number of lesions, it would be great to see how we can learn about some of these potential biomarkers, but I think that definitely will happen to be histology dependent. So what matters for lung cancer or colorectal may not have the same value for other subtypes like melanoma or CP or sarcoma, for that matter.

DR. VALLIERES: Yeah, Vallieres here. I don't have much to add. I do believe histology matters and beyond histology, I think the presence of a mutation that's actionable matters and we need to separate all of this. We're beyond histology right now, as far as the design of these trials, and to see whether --

(Audio feedback.)

DR. VALLIERES: We're going to be talking about DFI in the next question and I'm going to leave it at that for now.

DR. OFFIN: I think a lot of what we're hearing at the moment is that histology is important, the potential markers which are disease and histology specific are important. So

I guess from an ideal trial design perspective and how one actually would go for potential approval, it's going to be very nuanced. So I guess, like from a regulatory perspective, how would one go about trying to design a trial that was not just non-small cell lung cancer EGFR/ALK/ROS1 negative? And that could encompass other histologies or do we think that these would be separate individual endeavors?

DR. VALLIERES: I think that ideally they should be all separate, but we're not going to get there. We need volumes and we need numbers to get those trials to signify, mean anything. But ideally, I think yeah, they have to be very split, they're not all the same, and it's been said here and over and over again, not every lung cancer is the same, not every adenocarcinoma is the same, and if we do not separate these differences enough at entry, the results are going to be so mixed we won't know what to make out of it. So I think we're going to have to come to a very, very well-defined population when we ask those questions. Are we there yet? Not sure, but I think we're getting close to having where we're going to have to ask those questions in a very precise way.

DR. IYENGAR: I mean, the only thing I may add, if I could, is that I think the way that we need to really approach this, because these studies are taking too long, we all have a sense of urgency, we want to do the right studies but they're taking a long time, is probably to do more early-phase translational heavy studies, take 20 or 30 patients, similar histologies, similar biomarkers, collect samples longitudinally, get a better understanding of what the biology should be telling us and by doing that, it may better inform us about what are the more likely larger-phase trials that we'll actually see. I think that's one way of approaching the possibility of multiple histology type of trials.

DR. OFFIN: Very good. Are there any other comments on this specific question?

(No response.)

DR. OFFIN: I think we can move on to Question 3. Next slide. I'll just read it if they

could advance.

How does timing and clinical setting of occurrence impact the definition of OML? And I think to start off, we can have Dr. Conley to speak on this.

DR. CONLEY: Yeah, I mean, while I do think that histology plays an important role, I think most of us would have the same sense, I mean usually, like in sarcoma, for instance, having a patient develop oligometastasis in less than a year out from resection of primary is not usually a good clinical sign. I think there's been a number of small series published on pulmonary metastasectomies and other techniques that seem to show the same thing, that 1 to 2 years is that sweet spot and beyond to consider for a particular local modality.

I assume that the same is likely for the tumor types, so I realize that there might be differences. So I would say that it is important to stratify patients carefully, I think that if you have someone that develops oligometastasis rather quickly, personally, I would favor an approach that would involve a systemic therapy followed by the possibility of the localized consolidated therapy, I mean, that in itself could be like a study for patients in that situation. But I think for a more cleaner "get to the finish line first," I think we need to focus on the patients that have the better prognosticators to begin with and just try to refine it and improve upon that scenario.

DR. IYENGAR: I'll just continue with the thread by saying that I think we would all agree that for most disease primary entities, synchronous and metachronous metastatic disease represent two fundamentally different biologic entities and I would argue that's why sequencing becomes important. Unfortunately, we've had to be pragmatic in these trials in order to enroll to these trials and so we've ended up mixing synchronous and metachronous patient populations, less than ideal, based on the differences in biology. But I think sequencing is very important. If you think about non-small cell lung cancer, we know that radiation can alter, for instance, tumor, immune microenvironments can change for

potentially response rates of metastatic to immunotherapy. And so whether you do things sequentially, concurrently, at the time of synchronous versus metachronous, that all ends up being, as someone described, different nuances to add to the puzzle and I guess that adds to the complexity of the answers that we're trying to provide.

But I do think that what Dr. Conley mentioned about the timing between metastatic disease from the original treatment of the primary or so forth also biologically and fundamentally makes a big difference, as well. At the end of the day, synchronous metastatic disease is a snapshot, it's a snapshot at diagnosis and it doesn't necessarily mean a lot, which is why a lot of our non-small cell lung cancer colleagues have decided to do things at the setting of consolidation, then oligoprogression, rather up front and so time will tell if we're right or not.

DR. OFFIN: Dr. Harpole, any comment?

DR. HARPOLE: Sorry. No, I think I agree with what everyone else has said about this, it's pretty straightforward and we've had a good discussion.

DR. OFFIN: I'm curious in terms of people's practice, if you see a lot of like induced oligometastases or somebody that was oligometastatic had a really nice response to immunotherapy and let's say is left with two minimally PET-avid lesions. You know, in our setting we do consider consolidating those, if the person again has kind of proven themselves with time to have a robust and prolonged response, but how would you consider integrating something like that into this type of the trial?

DR. IYENGAR: Is that a toss-up or is that to me?

DR. OFFIN: A toss-up. I won't put you on the spot.

DR. KAVANAGH: Well --

DR. CONLEY: I think this is great compared to -- sorry. Oh, I'm sorry.

DR. KAVANAGH: No, please.

DR. CONLEY: Yeah, I think it would be great just to judge the data from these molecularly-driven trials. I would bet there's probably -- there would probably be enthusiasm from a number of sponsors to at least look at that, right? I mean, it doesn't happen as often in sarcoma, but for non-small cell lung carcinoma and some of the other subtypes like thyroid, it would be a real interesting issue to dictate future design.

DR. CAMIDGE: My two cents is if we're assuming that there's some kind of a randomized study, then having massive heterogeneity in terms of histology or systemic therapies is just going to make it uninterpretable. And so if you're also saying well, this is oli-progression, sorry, oligoprogression versus oligo-residual versus oligometastatic up front, again, they're likely to be on different systemic therapies. So I think in order to not end up with a study which essentially says this doesn't matter, which doesn't benefit anybody, I think we have to at least narrow it down to, I think, the same systemic therapy in the same setting.

DR. VALLIERES: If I may add -- go ahead, Brian.

DR. KAVANAGH: I was just going to say, so I think we need to show the slide or a portion of one of the slides was from where the AORTC (ph.) consensus statements that give this taxonomy, and Ross was hinting at it, the idea of oligoprogression, oligo-residual, oligorecurrent, that there is this matrix of potential classification of all these things and so it would be good to avoid that. On the other hand, in a practical sense you want to get a lot of patients in there. I think the advantage you have now is that you have these agents which are now out there, so solid, so well-established immunotherapy agents that are there for -- and I thinking broad categories you might be talking about immune -- you know, checkpoint inhibitor-based treatments for this kind of whichever histologies you now agree that worked for. So I can almost see it starting from immune checkpoint inhibitor resistant to oligoprogressive stuff. Boom, there you go. I mean, a lot of them would be lung cancer

and all the other cancers that are resistant to that or responsive to that, I should say. And then maybe there's a TKI bunch. I know it would be imperfect to have melanomas included with TKI-sensitive non-small cell lung cancers, but that's just a result that would probably fall out. So maybe the backbone of the systemic therapy is the stratification, I'm just throwing that out there.

DR. HARPOLE: This is becoming more unclear in a good way because we actually have options now, but I worry that we're going to pigeonhole this down into a small number of patients if we -- you know. And to tell you the truth, because you had to ask me if I had somebody show up with three new lung nodules and we know what they are, say they're colorectal, are we going to ablate them or are we going to try the next level of therapy based on their targets? I mean, I don't know what the right answer is.

DR. VALLIERES: If I may just add some comments about the DFI question. DFI is historically the very crude way of determining biology in the cancer. Not every cancer that presents with synchronous mets is going to be a bad player, some of them have decent biology, we just pick them up at this time and they looked like they are synchronous. Statistically, you're right, every study that has compared synchronous versus metachronous, the metachronous group wins. Why?

Because we've fused out a bunch patients who if we had waited, they would've just blossomed and we would have said you're not a candidate for surgery or radiation. And on the other side, when they come to us 2 years later, we have a damn good handle on their biology, they haven't blossomed and we know -- so what we need is we need a better way of determining that particular aspect of their biology at diagnosis because some of those patients are not going to do bad even if they present, at the beginning, with metastatic disease. DFI has just been a very crude way historically of picking who's going to win, who's going to lose, and until we have a better tool, that's what we have right now. That's just a

thought, I'm not answering your question, I'm just saying if someone wants to do research out there, this is something that's key, that's really important. If we had somehow a way of determining that aspect of the biology of the cancer at diagnosis, we could potentially open that up to patients who present with Stage IV disease at presentation and offer them more local therapies. A thought.

DR. CAMIDGE: That was a good point, Eric. I want to throw one other thing out because as we start to talk about opening it to everyone who might be amenable to any kind of local therapy, we should think about some of the endpoints. So if your endpoint is safety or local control, I think in theory you could have that open to anybody. But if you're looking for a systemic endpoint, survival or disease-free survival or something, again, that's where you could narrow it down. So you could have a core group which is randomized where you're looking for a systemic endpoint. If you're just looking for these local endpoints including safety, then you can have another companion trial to just throw anyone you'd like in.

DR. OFFIN: Thank you for that. I think with that we'll go to the fourth question. Next slide.

So this is kind of like a grab bag. What other parameters in your specific specialty are used to define OML? And then I think to add, are there specific parameters you think are useful from a correlative perspective that we should consider building out? I know ctDNA has been referenced, there's a lot of disease specific correlatives, as well. So I'll open the floor for discussion.

DR. CAMIDGE: I wanted to throw one thing out which --

DR. OFFIN: Yeah.

DR. CAMIDGE: I want to throw one thing out which strangely enough, we haven't mentioned, which is, I do think, in order to define oligometastatic disease, we have to

standardize the staging investigations which are done. So if you're doing it with CT and not PET, I don't buy that as oligometastatic disease, for example, so I think any study has to have that upfront written in.

DR. HARPOLE: It's an interesting question but by definition, we're a multimodality field in thoracic oncology, so I would wonder if any of us in a vacuum would have our own rules and things about this, I think we kind of do this as a consensus amongst all of us, wouldn't you all agree?

DR. CAMIDGE: I agree. Actually, one of the things, I give one of the recorded talks tomorrow, but one of the things I've said is it's going to be impossible to isolate the effects of one local ablative therapy versus others because in an individual patient, maybe you're going to resect one lesion, Puneeth's going to irradiate another, and someone else is going to ablate something.

DR. IYENGAR: I totally agree with what both of you have said. The other thing that I would just like to throw out is that at some stage we need to also account for toxicity, it's something that we always do account for. But I will tell you that if we're specifically in this panel talking about oligometastatic to the lung, I think we need to be a lot more involved in thinking about pneumonitis, you know, other metastatic disease sites I'm not so concerned about. But the issue with, for instance, lung cancer, when you're treating oligometastatic disease, is that if you're treating the primary disease plus another few oligometastatic sites in the thorax, you start treating a lot of lung and that, in combination with immunotherapy, may pose some challenges down the line. And so we've treated a lot of patients here at UT Southwestern on LU002 in some other trials, but I think it's something that we always need to constantly continue to evolve to understand which patients -- and this goes back to biology again, if we could predict which patients will have a worse or better toxicity profile based on some of their host tissue biology, it would be probably exciting to know about.

DR. VALLIERES: I will --

(Cross-talk.)

DR. KAVANAGH: Sorry.

DR. VALLIERES: Yeah. Hi, Brian. We just keep -- you go again. You go.

DR. KAVANAGH: That's okay. I would say although this is not exactly the question you're asking because you're asking for definitions, I do think that what was hinted at maybe by Puneeth a second ago or others is that there's an anatomic consideration here. Certainly, with radiation we are more alert to tumors that are touching or are very close to the mediastinum, adjacent to esophagus, large vessels, etc., and if one of the questions that is going to be possibly considered is the safety and efficacy of new modalities of treatment, there might be ways to look for specific tumor populations where other modalities are particularly tricky. And I'm just throwing that out there because the sort of ultra-central or para-central or centrally located ones are always a little bit of an extra cautionary tale that we have around those, but that wasn't exactly the question you asked. But anyway, go ahead, Eric.

DR. VALLIERES: To build on Puneeth's comment, we're dealing with Stage IV patients here, so I think quality of life has to be a parameter that will be included before, during, and after all of these trials. You cannot not include that. Number one.

Number two, going back to nodal disease, I think that has to be commented on, whether or not -- and again, it depends on the primary. I know the AORTC definition does not include metastatic mediastinal nodal disease as a site, I agree with some histologies, I disagree with others. And then what about someone who's lucky enough to present with five mets all in one lobe? That's a different player than someone who presents with five mets in five different lobes. That's back to your anatomy, not that many patients, but these things have to be taken into consideration.

DR. OFFIN: Okay. If there are no other comments, I think the next step here is we open the discussion up to attendees.

DR. VALLIERES: If I may make just one more comment and announcement, I badly need a thoracic medical oncologist here. If you're interested, please e-mail me. Seattle is lovely and that was it, thank you.

DR. KAVANAGH: He's not talking to you, Ross. There's no point to that.

DR. HARPOLE: It looks like Ross has got some lock on that door, anyway, so I don't think he's leaving. There you go.

(Laughter.)

DR. HARPOLE: I think we're all excited about the potential of these new technologies as an adjunct to treating our patients and I think, as Eric said, and certainly for palliating and for symptoms and so forth, control and potential, you can use the same word for cure. And I think it's how this is going to fit in the quiver for us to know when to pull the arrow out is going to be the question and -- because this is not going to be a panacea for everyone, but I do believe there are patients that could benefit from this and I think that, you know, Eric pointed out, you have three lesions in one lobe versus three lesions in three different lobes, central lesions.

I mean, I think we could come up with patients that could be favorably treated and again, bronchoscopic directed device that's more -- would be, I think, ideal for a more central thing that might be more difficult for radiotherapy, I mean, you could argue that. So I think that we could come up with patients, but I do believe it's going to be important for us to consider how this is going to fit amongst everything else.

DR. IYENGAR: Yeah, to continue Dr. Harpole's comments, I would say that at the end of the day for all of these patients, independent of the primary cancer, it is a multidisciplinary approach that will be optimized for the important types of treatments that

we're trying to suggest. I certainly think the other thing we need to consider is that with improved systemic therapy, these patients are living longer and longer and longer, and so what does that mean? You know, in our field of radiation oncology, I keep harping to my residents and others that we need to start accounting for treatments we did 6 months ago and then treatments we did 2 years ago and treatments we will potentially do a year from now. I know trying to predict what treatments we're going to do in the future and so forth is a little bit nebulous, but these patients are doing great, they're going to continue to do better and better, and so local therapies will become -- continue to be important.

And so that's why, as Dr. Harpole and everyone else on this committee and panel have mentioned, understanding when to use radiation, when to use a device, a bronchoscopic device, when to use an ablative or radiofrequency type of device management, when to use surgery and when to just stick with systemic therapy will become the ultimate question, but I think it's the integration of all of those treatment modalities that will optimize the benefits that we're looking for, for our patients.

DR. HARPOLE: I only have one comment. I'm David, my father was Dr. Harpole.

DR. IYENGAR: Appreciate it. Sorry about that.

DR. OFFIN: Other thoughts or comments? I know we're kind of early on time with only the four questions.

DR. KAVANAGH: Puneeth, let me ask you a question, if I could, about -- can you just remind me, because we've put a few people on your study, but is it -- what about the crossover, if you will, or the immediate versus delayed therapy concept. In a practical sense with some of your patients, how do you approach that? When you do informed consent, do you say that --

DR. IYENGAR: Yeah.

DR. KAVANAGH: -- down the road if something happens, we could still potentially do

something?

DR. IYENGAR: Yeah, yeah, yeah, I do. I say this study that we're trying to investigate and the LU002, we're really trying to ask the question of whether local therapy at this point in time, i.e. consolidation, we describe it in lay terms, is valuable. This does not shut the door on local therapy at some other point in time. I think, in the most perfect of worlds, for trial design we wouldn't have that opportunity, but that's not reality and that's not what we should probably be doing for our patients.

There will be patients that progress, that have oligoprogression and if that's the case, I tell the patients look, we've answered the question about PFS, we still have a question about overall survival, but hey, when we're trying to optimize your overall survival, everything is open, every option is open. And so if your medical oncologist sends you back to me, even though you were on part of the study that only was allowed randomized systemic therapy at the point of what would be considered consolidation, I'm very happy to consider treatment for oligoprogressive disease. So that again, as Brian here mentioned, is another limiting effect, potentially, on some of our outcomes but I think that that's the reality.

DR. CAMIDGE: Yeah, one just in terms of endpoints. One of the things that the Gomez study and some of our local ablative therapy for oligoprogressive studies have been criticized for is that we're just sort of Photoshopping the scans, you know, we take the lesion off and you evaluate it to this scar. And so one of the nice things in the Gomez study was one of the endpoints was time to distance or new sites of disease and I think we should think about that as an earlier endpoint in overall survival in some of these randomized studies.

DR. KAVANAGH: And then maybe minimal residual disease or circulating tumor DNA will also be a surrogate for that outcome, as well, so that could be helpful, as well.

DR. HARPOLE: Not to be a nihilist, though, I don't want to undercut the therapies because if you control disease in the chest from palliation, that's pretty good. I mean, a lot of these lesions will get necrotic and infected, all these kind of things, and so controlling them, I think for potential for quality of life thing for patients is not unreasonable, even if they have relapsed in other locations.

DR. KAVANAGH: Yeah, quality of life endpoints are totally legit, should go alongside -- it should go without saying, I guess, nowadays that patient reported outcomes, quality of life, everything -- some of that, sure.

DR. CAMIDGE: Well, the other thing that Brian and I have been talking about is how -- who we have data in terms of the safety of being on a systemic therapy when you do these local ablative therapies. So I mean, we are here talking literally about integrating multimodality therapy and it's not just the acute toxicity, are we going to change the rate of pneumonitis, as Puneeth mentioned, if it was in the brain, the rate of radiation necrosis, so I think we need to really up our gain in terms of capturing toxicities here.

DR. CONLEY: One other point I was just going to make is just the trial design. In the sarcoma world, because we're dealing with such small numbers, we always have to think about ways to innovate with regard to statistics and whether it's using adaptive Bayesian design or I guess there's been interest in the breast cancer world, like I-SPY, and these might be modalities or I guess, statistical measures to consider, if for instance the FDA is willing to consider some of these alternate types of -- I mean, clearly, if you're going to do Bayesian design, you have to have some prior information regarding how well some of these things work at baseline, right? So it's only as good as the information you feed into the equations, right? But on the other hand, with adaptive Bayesian design, you have the ability to potentially not need a very large number of patients to help identify oh, there's a benefit in terms of whether you're using a surgical or radiation comparator to one of these

particular types of devices. Or like for instance, like we do in Phase I where we have bucket trials where you're looking at a drug but in different histologies and the same alteration. So perhaps designing a study where yes, you claim to look at non-small cell lung carcinoma, or an RTC, for instance, and hopefully have a sarcoma arm for those of us that do sarcoma, but at least that way you can get cleaner readouts for each of these subsets and not just have everything skewed into one mass of patients where we could get results and questioning them in like a decade or so.

Obviously, if there's a little bit for frustration on our side, some of that is something that we see all too often and so having clean, good statistical measures will help, I think, in terms of reaching an understanding as to whether we believe the results will be negative or if we think they're positive, but positive because of the right reasons and not for some bias that was placed into the design. So it's definitely important to make sure you have a statistician involved and understand the right variables that you're going to put into the model.

DR. CAMIDGE: I had a surgical question which may perhaps just reveal my ignorance. So how good is the data in terms of what the margin you need to do for a metastasectomy in the lung?

DR. VALLIERES: David, do you want to take a shot at this?

DR. HARPOLE: Yeah, I guess it depends, it also depends on histology, as well. I mean, you want to err on preserving lung function and so I think nothing less than a centimeter, but I wouldn't go -- I don't think we need 3 cm. You know, the dictum for lung cancer is you want to take the diameter and at least have that as a margin, but for these, I think we tend to err a little closer. Eric, what do you think?

DR. VALLIERES: I don't have a lot of scientific data except that there's a procedure called the Perelman procedure which was designed by a Russian surgeon, I hate to use that

word these days, but it's a cautery dissection where you basically -- you're kissing a lesion and you don't have much of a margin at all and it's all cauterized and -- which pathologists hate -- and the results of that procedure, at least in sarcoma, are actually quite good. So I don't think you need a big margin. I think, as long as you have a clean margin, it suffices, but I don't know much more data than what I've just talked about.

DR. KAVANAGH: Well, I'm not a surgeon but -- and Puneeth might know this data, too. About every 5 or 10 years a paper comes out that winds up in the radiation literature that has to do with looking at specimens and how many millimeters away from the gross disease does the finger-like extension go, and it's often surprising that sometimes it goes further than you may think because we might not necessarily consciously go after a very large margin, you know, margins of the sort of prescription dose have been as small as 3 mm around the gross disease.

Having said that, everyone counters the argument with well, there's a gradually enlarging cloud of dose that goes a little bit further around it, so maybe it's catching those finger-like extensions. So there's chit-chat about that. If you look at it, you'll see a few millimeters here and there for sure.

DR. IYENGAR: Yeah. No, exactly, Brian. Every few years we reassess what those margins are. When I was training at Anderson, it was about -- you know, we always said maybe 7 mm but that changes, that can change with different pathologic series. You know, one comment that I want to make, it's very interesting to me is that with LU002, every time there's a new -- so we're agnostic to systemic therapy and again, to be pragmatic -- and so every time there's a new -- which is a great thing, new FDA approved IO-containing regimen, we amend the trial to include that. We think about the statistics of not comparing Phase III studies but what were the outcomes in the study that got the FDA approval, is it really okay to mix?

And part of the reason we're agnostic, well, part of the point of being agnostic is to be as open as possible to patient enrollment and to different combinations. You know, would it have been good to use one combination? Yes. But the question I have is if we find a benefit and if 90% of the patients on this trial are pembro-containing regimens, can we extrapolate this out to ipi-nivo combinations or atezo, it's a question that I've always had and just not sure what the answer is.

DR. CAMIDGE: I think there's a difference between what the medical oncologists would view and what the FDA might view, so I think medical oncologists would say sure, let's lump them together and the FDA is like prove it individually, but, you know, we have FDA people on the call.

DR. DREZNER: Yeah, I mean, I think we tend to not do cross-trial comparisons or comparisons of separate regimens to each other, so I think that that would probably be an issue for us, but I think that's not to say that there's no way that it could be done. I'm not super familiar with the study that you're talking about, but I do think that -- you know, we do have -- or that we have seen studies where there are multiple different regimens used prior to a common intervention and so I think that some of the ways labeling works, it tries to cover for some of those things. But yes, in general, we don't like to see cross-trial comparisons or comparison of one regimen versus another even if they're both immunotherapy-based regimens.

DR. OFFIN: Very good. I think that brings us just to about the end of the hour, so I want to thank the panelists for their attendance and discussion, the FDA for giving us this forum, and all of you in attendance, and I think we'll close there. Thank you.

DR. BLAKELY: Well, thank you, Dr. Offin, and thank you so much for all the panelists and speakers, this was a really great discussion.

So we're now going to transition at 3 o'clock and we are really extremely excited and

grateful to hear in our next session from patients with OML as they share their stories in a panel discussion moderated by Tracy Gray, the patient engagement lead in the Center for Devices and Radiological Health, and Dr. Christopher Eger, a thoracic surgeon and medical officer for the Respiratory Devices Team, which will start at 3 o'clock. Thank you all.

(Off the record at 2:56 p.m.)

(On the record at 3:00 p.m.)

DR. GRAY: -- patient perspective session of our workshop. Panelists, please turn on your camera if you have not already. Our panelists for this session are participating voluntarily. None of them has any financial conflicts of interest to disclose that are relevant to this workshop.

Good afternoon, my name is Tracy Gray and I'm the patient engagement lead in the Center for Devices and Radiological Health, also referred to as CDRH. At FDA and in CDRH, we believe that patients are experts on their conditions and offer valuable information about living with their condition and its treatments. Patients' perspectives can significantly impact the development, evaluation, and monitoring of medical devices. With great appreciation for the value that the patient's voice brings to the regulatory environment, it's my pleasure to welcome you to our patient panel discussion.

You will hear patients with oligometastases to the lung, which I will refer to as OML, share their experiences with what it's like to live with this condition and its treatments. Their perspectives will inform FDA's study design considerations for using transbronchoscopic thermal ablation devices and innovative technology designed to treat patients with OML. The panel discussion will be moderated by myself, along with Dr. Christopher Eger, a medical device officer in the Office of Health Technology 1, which is the office that has regulatory oversight of these new technologies. Dr. Eger is also a thoracic surgeon with more than 25 years of surgical expertise, treating patients with OML.

Before we begin the panel discussion, our patients will introduce themselves, give you a brief overview of their disease experience, before sharing thoughts about how they've been impacted by OML and what treatment aspects are important to them when considering transbronchoscopic thermal ablation devices. Following the patient panel discussion, Dr. Eger will give brief closing remarks.

JEANETTE: Hello, I'm Jeanette from Austin, Texas and I am a retired chemist. I'm here to tell you my story today. It starts back in 1990 when a month after my wedding, I was diagnosed with cervical cancer and had a complete hysterectomy, radiation, and chemo. Upon being released by my physician in New York, he said if it ever returns it will be a long time from now and by then, time will have given us better treatments. So here we are.

Two thousand fifteen, a lump was found in my abdomen, the diagnosis was leiomyosarcoma, which is a very rare and aggressive cancer. After traditional treatments of chemo, CT scans, and even a couple of surgical ablations to the lung, because it had spread to my lungs, we began to think of something different to try. That's when I became acquainted with IR ablation and since then I can tell you that I've had three of those treatments after we had tried even surgery and I would call lung ablation in the classical way.

We are now doing the IR approach. And in my mind, the comparison is stark because with the micro-cryoablation. I have less pain, less invasive, less anesthesia, less time in the hospital, 2 days only to maybe 5 to 6 with surgical resection. So to my mind, I'm back on the road much quicker. This means a lot to me because although the diagnosis has been devastating, it affords my husband and me a chance to be with family, with friends, where we can laugh a lot, we can share travels and restaurants and stories and continue our community work. So for me, it's like a Spanish classic toast, which is "Salud, pesetas y

amor, y tiempo para gastarlos." "May you have health, wealth, and love and time to spend them in." Thank you.

SAM: Thank you. Hi, everyone, my name is Sam. My cancer journey began in 2019. I had just graduated from grad school in June. Around August, I actually moved to a new city across the country, was gearing up to start my dream job, and I started having digestive issues, I thought it might related to stress. Eventually, a month or two went by, the digestion issues got worse and worse. I started my new job, I couldn't actually get a full workday in because of spending so much time on the toilet that I saw a doctor, they initially tried antibiotics and then eventually, we went with a colonoscopy when we couldn't figure out what was going on and couldn't make the issues resolve. During the colonoscopy, they immediately saw a tumor in my rectum.

A few days later I did a PET MSCT scan which identified a few sub-centimeter lung nodules, so we saw that it had spread also to some local lymph nodes. So the bowel and digestive issues were kind of the only symptoms I had, they were pretty severe towards the end leading up to the colonoscopy, there were no real lung-related symptoms that I had noticed; I was pretty active, exercising, hiking, all those things. So in terms of treatment, we started with 4 months of FOLFOX starting in December of 2019 and went through the end of March 2020, so COVID had started right towards the end there.

I then did 5 days of pelvic radiation in April, that was actually supposed to be a 6-week chemo/radiation regimen, but we ended up shortening it to just 5 days due to COVID, they wanted people not going in and out of the hospital so much and they wanted people kind of just to stay at home more. Then in June, I did the LAR surgery, the lower anterior resection, the pelvic surgery where they took out about half of my rectum and my sigmoid colon. Three months later we did the ileostomy reversal, which is kind of a follow-up to the lower anterior resection, that went well. Since then I've been regaining bowel

function in a really great way and I've been able to get my quality of life back up. Since then, as well, we've been treating the lung nodules. So starting in December of 2020, we did the first set of ablations across both lungs, I think there were maybe five or six nodules scattered across both lungs. The nodules were about 6 to 8 mm at diagnosis and they had come down during chemo to maybe 3 to 5 mm. However, once chemo was over, we saw, after a little bit of a break, some of them started to re-grow, so we decided to go after them through ablations.

Then, 6 months later in June 2021, we saw that a couple new spots had emerged, so we went after them again with ablation and similarly, in November of last year, rather than going back on chemo, I have definitely enjoyed having the option to just go after these spots directly with ablations, definitely easier recovery and easier on quality of life. In terms of quality of life now that I'm about 2 years out from the surgeries, it's been pretty good, obviously still some lingering changes to my bowel habits, but full control and definitely able to kind of live a high quality of life, exercise, be active. You can see on the next slide there, I'm still able to go hiking, I'm still able to go out skiing in Colorado and Utah, I was just in Breckenridge, Colorado last month, and I'm really happy that I'm able to do all those things and still live my life. Thank you.

JULIA: My name is Julia and I'm a 42-year-old wife and mother of four young children. I work as a marketing director and I live in St. Louis, Missouri. In July of 2019, I was diagnosed with undifferentiated pleomorphic sarcoma of the left breast. My cancer was localized in diagnosis. Unfortunately, 3 months later, my cancer returned to my left chest wall. Fourteen months after my original diagnosis, my cancer metastasized in my left lung. Although I've had three tumors, the only symptom I've ever experienced throughout my cancer journey was the initial symptom that sent me to the doctor, an enlarging, painless breast mass. My primary tumor was removed with surgery and 40 rounds of

proton radiation therapy over 6 weeks. My first recurrence was treated with surgery and five rounds of adjuvant chemotherapy. My lung metastasis was removed via a mini-thoracotomy procedure. I consider myself lucky to have stayed disease free since my thoracotomy procedure 18 months ago. My diagnosis disrupted my mental, emotional, and physical quality of life. Physically, I'm two and a half years into my cancer journey and despite multiple rounds of physical therapy, I still struggle with a limited range of motion on my left side and this leaves me unable to do many of the core activities that I enjoyed pre-cancer, like playing tennis and lifting weights, particularly lifting weights overhead.

Today, day-to-day movements and tasks that involve reaching for, lifting, or carrying things overhead are difficult for me to do independently. To this day, I continue to do mobility exercises, I get deep tissue massages regularly, and even acupuncture to help break scar tissue and to maximize my range of motion. I believe these additional therapies have helped keep my quality of life higher than normal for someone in my position.

SAMANTHA: Hi, my name is Sam, I live in London in the United Kingdom. I'm an operations manager for a firm of chartered accounts, a job that I love and have been there many years. Prior to my diagnosis of lung cancer, I led a very active personal social life, enjoying holidays, family time, friends time, and several holidays a year. And in March 2018, I was diagnosed with an adenocarcinoma of the lower right lung. This was followed in X-ray due to a persistent cough, which was the only symptom I was experiencing.

I underwent a lobectomy to remove the tumor and started adjuvant chemotherapy shortly thereafter. Following several months of chemotherapy and immunotherapy trials, a CT scan was carried out and discovered the cancer had metastasized and I had three further tumors in three separate lobes of my lungs. Following this, I started chemotherapy and in January 2020, I had my first microwave ablation surgery on one of my tumors and CyberKnife radiotherapy on two further treatments. Following this, I was on maintenance

chemotherapy in April 2020. In May 2021, while still on chemo, a further tumor was discovered and a planar CT showed that another tumor was on another lung, in my upper lung. I underwent microwave ablation on both lungs at the same time; the first time this was carried out by my specialist. I was diagnosed with non-metastasized breast cancer in July 2021 and started breast chemotherapy to treat this and had a mastectomy -- I spent the last 4 years receiving surgery, chemotherapy every 3 weeks, numerous scans and appointments whilst working full time, which is very important to me.

This is very much a balancing act. Treatment has changed my life in the way that I look due to hair loss, weight gain, and general fatigue. Socializing is affected because the taste in drinks and food are not the same to me anymore, and fitting treatment and appointments around my life impacts work, social life, and the holidays, but I'm here to tell the tale. I look forward to participating further and answering your questions.

NANCY: Hi, I'm Nancy. My son is Sam. He was diagnosed at the age of 18 with Ewing sarcoma back in 2017. Sam was referred to as "Beast" in high school. He's a very active young man. He loves to camp, hike, climb mountains, anything outdoors. In 2017, he experienced some minor pain in his knee, which we dismissed because he was so active, but then one day it reached a level 10, we took him to urgent care, and they diagnosed him with osteomyelitis, which is a bone infection. They told us there was a one in a million chance that he had cancer.

So after 5 days of intravenous IV, they came in and said he did have Ewing sarcoma. That began our journey of four and a half years where he received the first year 7 months of chemo, 14 cycles of five different chemos. In the middle of that, they had to remove or replace his knee and five inches of his femur, which is where the tumor was growing. He was clear from cancer for about a year and then, a year later, after chemo, one lung nodule appeared. Through the next 4 years, lung nodules reoccurred several times. We used

chemotherapy, radiation, multiple surgeries to reduce the tumors. He currently has no evidence of disease and we're thrilled. One thing he's requesting is to please look for new technologies so that he doesn't have to continue to be pieced apart. Sam is still hiking and biking and doing all of the things he loves, just not quite at the level he used to, but he is a wonderful young man. Thanks for letting us participate.

DR. GRAY: Thank you, Jeanette, Sam, Julie, Samantha, and Nancy, for introducing yourselves and for sharing that brief overview of your very complex journey. We look forward to hearing more about your experiences during our panel discussion, starting with the first question that each of you will have an opportunity to answer.

Question Number 1: How has your diagnosis impacted how you feel throughout the course of your illness, both physically and emotionally?

Let's start with Jeanette, followed by Julie, Nancy, Sam, and then Samantha. Jeanette, you might have to take yourself off mute.

JEANETTE: Thank you, Tracy. There you go.

DR. GRAY: Okay. There you go.

JEANETTE: Thank you. I think for two people who are retired and have a very small family, the diagnosis of cancer gives you a very outsized impact because you look just to each other for most of your support. So even though we feel bruised by this, severely bruised, we are not broken and of course, a lot of people will say no, our relationship is better, but it certainly is a two-person experience. The good thing is we have been so impressed by the clarity of the MDA staff in explaining options and why, and willing to take a leap to do the clinical trial with you, that we feel like all of this will maybe someday be beyond what we have been able to do for each other. Thanks.

DR. GRAY: Julie, and you?

JULIA: For me, my diagnosis has left scars, both physically and emotionally. First,

emotionally, I think cancer is a life-changing diagnosis that can be very difficult to cope with and I found that to be the case for me. I think, emotionally, cancer is very taxing because historically, the ways that we treat disease are relatively toxic, it can be degrading to one's quality of life and certainly, in the metastatic setting, have a relatively low track record of long-term success. And from my experience, I found that the mental and emotional side effects of cancer sometimes are left to the patient to kind of cobble together a coping plan, but patients aren't always equipped with the skills necessary to do this.

I found myself fortunate to have been treated at a major cancer center where I had access to mental health experts who taught me valuable coping skills and allowed me to thrive with my diagnosis. Physically, I feel like I felt a range of physical feelings throughout the last 3 years and how I felt physically often depends on the treatment that I'm pursuing at the time. I've had periods of no evidence of disease where I have led a very normal life. On the other end of the spectrum, I've had periods where I've been unable to sleep and unable to care for myself, as the treatments were so debilitating.

Over the last 3 years I've had multiple surgeries, radiation, chemotherapy, and all have impacted me in different ways. I won't go through all of them, but some of them have left longer-term side effects, so even today, from radiation, I still have discolored skin, I have radiation fibrosis that has caused stiffness and very limited range of motion that can sometimes be problematic for me. With chemotherapy, that was obviously the most physically debilitating. But in summary, how I felt throughout my diagnosis is really dependent on the measures that I've needed to take to treat my disease and the treatment and their associated risk-benefit ratios and the toxicity and quality of life, all of those elements have played into my physical state of wellbeing, as well as my emotional state of mind.

DR. GRAY: Nancy.

NANCY: Hi. My son, Sam, has been dealing with Ewing sarcoma for almost 5 years, as I mentioned earlier on the slide or on the slide show. The biggest way that it has impacted his quality of life is that because of the treatments that he's had to have multiple through these years, and most them, as Julie mentioned, are pretty archaic still, it stalled his life. He had just graduated high school when he was diagnosed and so every time, he started college three times, he had to drop out because of some treatment, radiation, chemo, combination of treatments.

So he's back in college, he has no evidence of disease now, but he, for a long time, will be emotionally and physically challenged because of the treatments and because he's still dealing with this. He also has, besides lung issues from the lung metastases, he has a prosthetic knee and femur that he has to deal with, as well. So for 18 years old, it's a big burden and it definitely stalled, changed his life. Probably one of the -- excuse me -- hardest things is he still lives at home, he just hates still being at home. So anyways, that's all. It's still hard.

DR. GRAY: Thank you, Nancy.

Sam.

SAM: Yeah, I can echo some of those sentiments from Nancy, as well. As a young adult, I was diagnosed with Stage IV rectal cancer at the age of 28 and I was an independent adult with a job and the next thing you know, I had to move back in with my parents and go through FOLFOX for 4 months, which was pretty difficult for myself, the whole family, obviously a very emotional time, and open lower anterior resection surgery also had me very temporarily disabled. The physical side of kind of what's going on through cancer treatments, I'm sure the doctors on this call know fairly well and they see that in their patients and the emotional side, as well. As a young adult in my late twenties going through cancer treatment, it's tough because you do put your life on hold and you're at a

stage in life where you see your peers around you kind of taking really positive steps, getting married, buying houses, having children, and for me, the stage of life I was at I was about to do all those things and now those things, I don't know if they can ever happen. So the emotional side of things, I think, is one that maybe the doctors appreciate and understand for some of their patients, but it's definitely very different depending on stage of life and I think, as a young adult in my late twenties, as a working professional who then had to kind of have a huge change of lifestyle, it was really difficult and so yeah, obviously finding professional mental health support is really important.

But, you know, dealing with OML now, it's tricky because I feel pretty good, I've been off chemo for 2 years, I've recovered from the surgeries, the ablations are fairly minimally invasive in terms of quality of life, but there's always that sneaking suspicion in the back of my head of what's going to happen, nobody can tell me, you know, every three -- I'm living my life 3 months ahead of time, scan to scan. If we see a small met, we go after it or we let it stay there, and it's just like I don't know if a year from now I'm going to be a normal 30-year-old adult or if I'm going to be back living with my parents on chemotherapy and that kind of uncertainty is really difficult for me.

DR. GRAY: Thank you, Sam.

Samantha.

SAMANTHA: Hi. I'm going to cite physical treatment, not cancer, has impacted me the most with my diagnosis -- chemo affects my ability to do many things I used to be able to do. My health has been affected by the chemotherapy, as I've had extra -- I have lymphedema and also the chemo damaged my heart so now I'm on medication to keep that under control. Emotionally, it's obviously very hard to cope with and I think the biggest emotional thing to cope with is the physical changes to your routine, how you look, it's in such a stark difference to how you want to look, you know, I look back at photos of myself

and it's a different person. I'm the same person inside, but I look like a different person. And that's hard, that's really hard for people to deal with. I'm very strong with being positive about the way that I deal with my diagnosis and I'm not in control of what happens to me medically, that stands with my specialists and they are the experts. The one thing that I can control throughout my four-plus-years journey is my attitude towards my cancer and being positive and making sure that I feel like it's fitting into my life, not actually dominating my life, and that's kind of the only way that I feel I can get through it.

DR. GRAY: Thank you, Samantha, and thank you all, panelists, for sharing those insights about how you've been impacted both physically and emotionally and we can just hear that it's a challenge and so we appreciate you sharing that with us.

Now I'd like to ask Jeanette and Julie Question 2: How has your treatment of your illness and symptoms impacted your day-to-day life? And has it impacted your ability to go to school or work, things like that, or how you engage with the community or just in terms of your daily tasks or social activities?

So let's start with Jeanette.

JEANETTE: Thank you, Tracy. I want to share camaraderie with my fellow panelists because I, too, have experienced all of those things. Day to day we took an experiment because we have kind of a pretty visible public life in the city where we live and people know us on sight or by name, and we decided, between the two of us, that we would not tell people my diagnosis from 2015 and yes, even though I wear a wig now, apparently nobody even noticed. So I was able to -- I call it go in disguise in a happy way and continue our life without a lot of curious or badgering questions or concerns from friends and acquaintances. So we've taken that path and it actually has seemed to work because the work is inside me, not outside in the public, and it seemed to work. I must say that there's a spirituality aspect to this, whether it's from yoga or from one's religion, that becomes very

real to me and it's hard even to share that reality with your partner because it's so personal and fleeting, even though an insight might be very profound. So that is one thing I can say, is how it has impacted me is that some of this is all inside, some of it you want to share outside but you can't, and I agree, more guides, tips, check-in from counselors might be a good thing, both for the patient and for the married or family/couple. Thank you.

DR. GRAY: Thank you, Jeanette.

Julie.

JULIA: In terms of how treatment has impacted my day-to-day life, it's taken me 18 months to recover from the continuous cancer treatments that I experienced over a time period of 15 months. I do consider myself very lucky to have had 18 months to recover both mentally, emotionally, and physically. Only recently have I felt a mental capacity to be able to think beyond myself and my own case and begin opening my mind to ways that I can be involved in cancer support or cancer care beyond myself.

I think I mentioned in the previous question that the way that these treatments have impacted my life really is dependent on the treatment that we're talking about. Some have had a very short window of interrupting my life, others are still sending me reminders, even 3 years after a treatment has ended.

I think one of the biggest lessons that I've learned is that I really need to take the lead in helping physicians understand how a treatment might impact my ability to do things like go to work or go to school or participate in community activities. A great example of this is, I know in my case, I had a physician tell me that he wanted me to continue working while I was going through a rather intensive treatment because it was good to "stay busy" and work is one way to stay busy. You know, for me, I don't know that I was a typical sarcoma patient and had to remind him that I have four young kids under eight at home, I had a demanding full-time job, and that the only way I would be able to prioritize health

and self-care during this time would be if I wasn't working and had the ability to rest and recover, which I felt was really vital to my healing. Luckily, I work for an organization who has a generous leave program where I was able to take the time I needed and then continue working once I was ready to return. I have been disease free for about 20 months now and so many of the impacts that I still experience, thankfully, are relatively limited. I do have range of motion issues that I talked about in my video that prevent me from doing some of the things that I used to do before my diagnosis, but other than that I feel like I have been able to lead a very high quality of life despite the various treatments that I had.

DR. GRAY: Thank you, both, Jeanette and Julie. I'm going to try to move quickly to the next question because we're a little bit behind, but thank you so much for sharing.

Nancy and then Sam, would you please respond to Question 3: How has learning that your cancer metastasized to the lung changed your life the most?

NANCY: Okay, for Sam, it changed his life because he went from doctors basically telling him that his chances of survival were very high, 80%. You know, they love -- some love to give statistics, some don't. Eighty percent that he would not relapse, he would be cured, he would go on. And when they found the first lung nodule, that greatly decreases your chances of survival and they let him know that and he researched it enough that he found that out. So it changed his whole hope that he could beat this and now it was something that he was going to have to deal with long term.

So really, it turned it from like climbing a mountain, a challenge, an individual challenge, to more of a constant battle. His lung nodules have reoccurred three times, so he has been undergoing some kind of treatment almost continually for 5 years. So it's been a real battle and mostly, it has affected him emotionally in terms of how he sees his future life. Physically, the lung nodules really haven't impacted him that much. He has had some symptoms occasionally from the lung nodules, but for the most part, he's still doing all the

things that he loves to do. So anyways, mostly it just took away some hope.

DR. GRAY: Thank you, Nancy.

Sam.

SAM: Yeah. I think similarly, with rectal cancer and metastatic spread to the lungs, on the one hand I try to stay optimistic because it is oligometastatic, there are a few mets, we handle them with ablation. Like I said before, I've been off of chemotherapy for 2 years and we've seen a very small number of very slow-growing mets pop up and they've been able to be treated with ablation fairly successfully. That's kind of the good view of it.

The bad view of it is yeah, I've had multiple lung metastases and it's Stage IV rectal cancer, so I try to stay positive, but I do understand that when there is spread to the lung, when you see continued growth in the lung after removal of the primary tumor, that's not good. I'm on what they call whack-a-mole, right, we see a nodule, we track it for 3 months and then we ablate it, that's kind of been the process thus far. I'm actually having a segmentectomy tomorrow because one of the nodules which we've had to ablate twice is still growing. I had a biopsy just 2 weeks ago where they confirmed that it is still alive.

So this is the first time we're having a surgical intervention beyond the interventional radiology procedures on this lung nodule because it's growing into the bronchus a little bit, which is unfortunate because I wish there was a transbronchial ablation device that was approved and successful and something that everybody -- you know, was just more commonplace because that would probably save me from a surgery.

So things like this are obviously a future that I want to accelerate, but all that is to say, you know, when you have lung nodules, it changes the game when it comes to colorectal cancer. On the one hand I'm trying to have as normal of a life as a 30-year-old can have, but on the other hand I know that there's this thing happening in my body and it's not fully treated. Yeah, I think after tomorrow's surgery I'll be able to kind of at least relax

knowing that there's no more visible cancer in my body; hopefully, it stays that way for a long time. The emergence of these lung mets, like I said, has been very few and far between but it's there, so the question is really is this going to stay as OML or is this eventually going to grow so much that we won't be able to go after it in the whack-a-mole strategy, that's the big open question that I'm kind of dealing with right now and after this whole surgery thing happens tomorrow.

DR. GRAY: Thank you, Nancy and Sam.

Now we'd like to ask Samantha and then Jeanette to please respond to Question Number 4: What does treatment success mean to you and your family?

SAMANTHA: Thank you. Having been diagnosed two and a half years ago with Stage IV cancer, I'm being told I will be treated palliatively. I never thought I'd be in a position where my oncologist believes that he can take me off of maintenance chemo, not because I'm cured, of course, but because he believes that he can manage any new tumors which will happen by ablating them instead of the constant drain of chemo and what that's doing to my body. So provided any more tumors to the lung are caught at the early stage, this may allow me to live longer than the current statistics in Stage IV cancer.

Obviously, this will also lessen the burden on me and my family. Currently, my sister drives me to my chemotherapy appointments, drives me back rather than using public transport, especially during the pandemic. And this, you know, has limiting issues. If I'm not having chemo every 3 weeks for the rest of my life, this will mean less disruptions in my work and allow for the scheduling around the holidays and time with the family. My type of ablation is also far less invasive than other forms of treatment that I've had. After all of my ablations I've been able to return to work or normal life the day after surgery with fairly little post-treatment effects. So for me, you know, the success is all of those things.

DR. GRAY: Thank you, Samantha.

Jeanette. Jeanette, is your -- are you on mute?

JEANETTE: Yeah, I think so. Testing, 1, 2, 3. For me, it was such a long road from 1990 to 2015 when, in fact, the real leiomyosarcoma, if it became -- was discovered, it was because it was right underneath a radiation line of where my first incidence of cancer was detected in a hysterectomy. So I knew those hours I had spent in radiation were a significant associated problem with the leiomyosarcoma. Besides just the anger of being let down in that situation of how could this have happened, it has really been dealing with the uncertainty, as Sam called it, the whack-a-mole approach to the success of the IR but also, I call it "watching for the next algae bloom" in the lungs, that these little things can disappear and then all of a sudden they're there again, a lot of them, maybe more than even before.

So I kind of wait in dread and now, of course, people are lining up, my oncologist, about saying well, maybe next time let's be more open to chemo. But it's usually a train car approach to things, try one thing, then we'll do something else, then we'll do something else, and my curiosity for chemistry is to say there might be some way to link the two therapies together to shorten not only the chemo, but make it maybe more effective if it followed very closely or concurrently with the ablation, IR ablation techniques, and I look forward to that. I keep looking for things that Dr. Allison of MD Anderson finds that may end up being very effective with leiomyosarcoma. It's just one of those very rare, very aggressive cancers that I'm sure I share with some of the others on the panel. Thank you.

DR. GRAY: Thank you so much for sharing that, Sam and -- I'm sorry, Jeanette.

So now we'd like to take Question 5: Have you received enough information on options for treatment and use of medical devices for your care? And who has provided this information and is there other information that you feel you need? So let's start with Julie and then Nancy.

JULIA: For me, I feel like I have been forced to make decisions based on risk-benefit

ratios and obviously, those boundaries are different for every patient, but the types of information that I typically want to know are things like a history of a certain treatment, how long it's been used, how long has this particular physician been using this therapy or how is it used in my specific cancer type. You know, certainly I look for information on the safety profile of a treatment, what side effects does the treatment provide, how are those side effects -- short-term side effects different than long-term side effects. I look for efficacy in terms of the outcome that the treatment is most likely to deliver, are we talking curative, are we talking palliative, and then how effective is the therapy at producing the intended results.

You know, I also think another thing that's difficult when it comes to Stage IV disease, and other panelists have talked about this, is the difficulty sometimes of comparing other treatments side by side, making an informed decision. I think this is where it gets tricky because we're reliant on different specialists to help us understand various ways that we can treat our disease.

So in terms of where I get information, I certainly use a variety of sources, particularly my medical oncologist and care team advising me, but I also find that speaking with other patients really provides a real-life viewpoint on a particular treatment, and it helps give me a qualitative perspective that balances nicely with the quantitative perspective of my oncologist and care team.

DR. GRAY: Thank you, Julie.

Nancy.

NANCY: Yeah, I have to echo a lot of what Julie said. For Sam, because Ewing sarcoma is quite an aggressive disease, we, too, have had to rely on multiple specialists, not just oncologists, and Sam, we've consulted with three, four sarcoma oncologists, he's had three or four naturopathic doctors through the years, specialists in Budapest at

hypothermia clinics. A lot of what I do, I retired 2 years after, from my job, after Sam's diagnosis, and I literally spend, I bet 80% of my time researching alternative methods to help keep Sam alive because just relying on what one specialist says or this standard-of-care treatment usually does not suffice to keep Stage IV Ewing sarcoma patients alive. Unfortunately, the mortality rate is quite high. Most of the kids, young adults that we knew years ago with Ewing sarcoma, have passed.

So one thing I wanted to point out from Sam, wanted me to interject today, was he said you know, I just don't want to be pieced apart anymore. So if there's a way that this panel, this technique can be approved and used in the near future as one of these tools that Sam and I spend so much time researching, that would really help patients with Ewing sarcoma. So again, we really reach across a broad depth of specialists and we try to put all the pieces together, like Julie said, and help our oncologists decide what's the best treatment. And so we're running out of treatments and your treatment may be another option or tool in our toolbox.

DR. GRAY: Thank you, Julie and Nancy.

We have three more questions and we're down to 12 minutes, so we're going to take the next question, I'm going to ask Sam and Samantha, and if you can try to respond within about a minute and a half each, that would be great, and then the following question, we'll only have five instead of 10 minutes to respond to.

So Question 6, Sam and then Samantha, please tell us what the benefit and risk considerations for a new device-based therapy would be most important to you.

SAM: Yeah, so I'm probably open to more risky new technologies and devices and treatments. A transbronchoscopic ablation device sounds amazing to me right now because I am 18 hours away from a segmentectomy. You know, if they told me tomorrow morning at Sloan Kettering that instead of doing the segmentectomy they could offer me the world's

first transbronchoscopic ablation with a leader in the interventional radiology field, I would take that. So I think for us, as a cancer patients, we are actually thinking about risk/reward differently than the doctors are. The doctors, they see it as where's the data, where's the evidence, you know, there's no evidence that this statistically can improve survival rates over 5 years, yeah, I don't really care. This sounds like a way to directly get at the tumor without having to take out my lungs. It sounds like something with an easier path to recovery, right? When I'm looking at my life and my disease, I don't really care as much about the huge datasets and the statistically significant evidence, I care about like the direct application of the science and the medicine.

I mean, I know that may not be right and I know that may not be the statistically smart thing to do, but personally, for me, as a young man trying to beat cancer, I'm willing to go a little crazier, maybe, about something brand new that may not be fully tested because the things that have been tested that I've gone through, they've also been really difficult and they've also been really risky, so how much risk are we really controlling? And maybe a lot and maybe I'm a little overbearing and sometimes I definitely am, you can ask my medical team that, but I'm okay taking a little bit more risk because I've already risked a lot and I have a lot on the line, so that's the way I think about it.

DR. GRAY: Thank you, Sam.

Samantha.

SAMANTHA: Very well put by Sam there, you know, I couldn't agree any more. As the first patient that my thoracic surgeon has ever completed microwave ablation on two separate lungs and he said well, this is risky, I've never done it before, I said go ahead, I trust you. There's always got to be somebody doing it first and I was very happy with that. I think, as patients, we're consulted on options that are very often available to us but they're invasive, they're chemotherapy, they're surgery, you know, radiotherapy, and

microwave ablation does have risks associated with it but, in context, they are just as risky as all the other treatments, but it is far kinder and more quickly effective. So it allows us to continue with our lives with very little time of disruption. And obviously, when you're being treated palliatively, that's really important, I don't want to spend all my time in hospital, I want to be out enjoying what's left of my life. And as patients, I believe we have to trust the medical professionals to put forward what they believe will help their patients and as long as the risks are discussed and you have trust in the treatment and I believe it wouldn't be put forward to me as an option if it wasn't effective.

DR. GRAY: Thank you so much. I appreciate that, Sam and Samantha.

So now we have 8 minutes left, so if each of the panelists could just tell us, within 1 minute or less, anything else that you'd like to share about your condition with the audience, starting with Samantha and then Sam, Nancy, Julie, and Jeanette.

SAMANTHA: Okay, as quick and succinct as possible. Cancer is a horrible and debilitating disease. I currently have two that I'm fighting and it is hard, you have to be very strong to survive, not just cancer, but the treatment, as well. So during my 4-year journey, I've had surgeries, radioimmunotherapy, chemotherapies, and as well as microwave ablation, so I have the ability to compare all the different types of treatment and I can honestly say that microwave ablation has been the least invasive of all the treatments to date that I've had. We've seen it in a world where the most effective form of treatment is so toxic that it, I mean, kills cancer but of course is extremely detrimental to other parts of the body. And so I'm a massive advocate for this form of treatment.

DR. GRAY: Thank you, Samantha.

Sam.

SAM: Yeah, I would say my heart goes out to, obviously, all the cancer patients. You know, I look around the waiting rooms in the hospital and it's really difficult to see everyone

and know that's a person with a life and a family and loved ones with career dreams and other dreams and everything that's kind of put on hold and even ending from cancer. I also am very aware of the role of the doctor in this and I feel for the doctors, too, because I know if they were to get emotionally invested in every single one of their patients, they would be unable to do their jobs, they would see so much death and so much suffering and be paralyzed. So I understand when my doctors sometimes keep me out a little bit of a distance, as frustrating as that is, I understand why they do it, but I still try to break through and I try to connect with them as people and I know it must be so difficult for them to hold back and not make personal, emotional connections with every single one of their patients because if they did, they would be burnt out within 2, 3 years once they see what actually happens to people with cancer after 3 to 5 years, right, I've seen the numbers.

So it's just a really, really difficult challenge and the doctors who are working with me are amazing humans who are doing a very difficult thing. The families, the patients themselves, you know, it's just really, really hard for us and we see a side of life that most people are blind to and that's just the way it is. But I'm so thankful and grateful for the doctors, the inventors who are pushing and accelerating the future, that's the thing that's nearest and dearest to my heart. Let's get to the future sooner because yeah, the current treatment options today, some of them are really good and some of they aren't and let's get to the future faster. Thank you.

DR. GRAY: Thank you, Sam.

Nancy.

NANCY: I think that one of the reasons, or the main, that Sam has survived this long has been because he has been doing multiple treatments. But having said that, he is tiring of doing all of these treatments. His body as well as his spirit can only take so many of these harsh treatments like chemo, radiation, multiple surgeries. So having something

available that's less intrusive, something that can give him a quicker recovery time so that he can live his life as a young person is really, really important. The last thing that he wants to do is spend more of his life in hospitals. He has spent probably, I'd say, a third of the last 5 years, if not half of his life, in some kind of treatment or hospital. So he is looking forward to this new technology and we hope it's available soon and for sarcomas, especially Ewing sarcomas, which sometimes have -- can be -- can track through the lung when they do a conventional cryoablation, that's why Ewing patients sometimes avoid that, cryoablation, which is radiation. But it sounds like this new technique may not have that same consideration and might be very valuable for kids like Sam and will give him hope. We just need it to happen quickly. So that's a question for the whole panel, is come on, folks, we're desperate. Thank you.

DR. GRAY: Thank you. Thank you so much, Nancy.

Julie.

JULIA: Yeah, I think I will echo what a few of the other panelists have said. I don't necessarily need to add more about my condition, but I would like to add that when it comes to sarcoma, the playbook is small. We don't have a lot of tools in the toolbox and we desperately need more. And so kudos to all of you who are fighting to get us more tools because they are desperately needed and they are needed quickly.

DR. GRAY: Thank you.

Jeanette.

JEANETTE: For me, I have a two-prong wish list since everyone else has said what I would be able to agree with and that is I wish that the manufacturers of this procedure, whatever brand is used, is that they would develop a sheet to give to each patient after the ablation because you can hardly believe how good you feel compared to what chemo and radiation and surgery have all done to you and you are almost unbelieving that this is

normal, that you will recover well and quickly. Do it to your credit. The second thing is, on my wish list is that I wish there was a way to show and prove that in the places where I have received ablation, IR ablation, there are no more nodules. We can't do my whole lung on both sides, but I was told there's like -- it's like a black hole, to which I said I wish we had a regression analysis of the lung to show the lifespan of those areas that were hit and those that were not and of what has occurred in the ensuing 3 or 6 months after that to show what has actually been retarded or stopped. But I understand right now there's no such thing, but maybe NASA even has a way from the black hole institute to help out on this. But those are my two wishes, there you go.

DR. GRAY: Thank you so much. And for the sake of time, I just want to tell all of you that we truly, truly, truly appreciate you being here today and sharing so much of your stories, which I know is not easy to do. Now I'd like to turn it over to Dr. Christopher Eger for closing remarks.

DR. EGER: Yes, I don't have much to add to what Tracy said. I just want to thank you all, as panelists, for sharing your very personal story about what it's like to live with or care for a loved one with this oligometastatic --

(Audio feedback.)

DR. EGER: Hearing your perspective is very important to us when considering innovative technologies used to treat oligometastases to the lung, such as our transbronchial ablation devices. It does provide great insights to the FDA as we conduct our business of regulatory review. The benefits, we see through the whole, all the stages of medical device product life cycle, including before it has received FDA approval, which is the status of this technology now. I wish you all the best with your medical condition and treatment. This concludes our patient perspective session and I will now turn it over to Dr. Eric Mann, who will provide closing remarks for the day.

Dr. Mann.

DR. MANN: Thank you, Chris.

This has been a really wonderful panel and many thanks to the patients and to Chris and to Tracy Gray for such an outstanding and moving patient perspective session, and it's so important for everybody at the meeting to hear how oligometastasis to the lung has impacted these patients' lives and what is important to them in terms of novel therapies for their condition. My name is Dr. Eric Mann and I am a medical officer and senior advisor in the Office of Health Technology 1.

In addition to the patients who participated in the last session, I would also like to thank all of the other stakeholders who shared their perspectives during this first day of our workshop. We heard from diverse professional societies representing the clinicians who are involved in the treatment of patients with OML, as well as manufacturers who have developed these cutting-edge technologies and which hold promise as a new treatment option for OML patients.

And we had a very excellent panel discussion regarding how OML should be defined for the purpose of future device clinical trials and I can assure you that all of this valuable feedback that we received today will be carefully considered by the FDA review team as we move forward with our regulatory approach and our oversight of these devices. So thank you again to all of the stakeholders from Day 1.

Now, tomorrow, on Day 2 of the workshop we will have three additional panel discussions. The first session tomorrow will discuss identification of an OML patient population suitable for transbronchoscopic thermal ablation treatment. We will next have a session on clinical study design considerations. And finally, we will finish up with a discussion of what is important for the assessment of transbronchoscopic thermal ablation systems. So please join us promptly at 11:00 a.m. tomorrow morning Eastern Daylight Time

and have a good evening, everyone, and this concludes Day 1 of the workshop.

(Whereupon, at 4:03 p.m., the meeting was adjourned, to be continued the following day, Wednesday, April 6, 2022 at 11:00 a.m.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

VIRTUAL PUBLIC WORKSHOP – STUDY DESIGN CONSIDERATIONS FOR TRANSBRONCHOSCOPIC THERMAL ABLATION DEVICES FOR THE TREATMENT OF OLIGOMETASTASES TO THE LUNG

April 5, 2022

Via Webcast

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

TOM BOWMAN

Official Reporter