FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Thursday, July 25, 2024

9:00 a.m. to 1:49 p.m.

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

Introduction of Committee

DR. SPRATT: Good morning, and welcome. I would first like to remind everyone to please mute your line when you are not speaking, and also a reminder to everyone to please silence your cell phones, smartphones, and any other devices if you have not done so already. For media and press, the FDA press contact is Lauren-Jei McCarthy. Her e-mail is currently displayed.

My name is Dr. Daniel Spratt, and I will be chairing this meeting. I will now call the July 25, 2024 Oncology Drugs Advisory Committee meeting to order. We'll start by going around the table and introducing ourselves by stating our names and affiliation. We will start with the FDA to my left and go around the table.

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

DR. KLUETZ: I'm Paul Kluetz, Deputy

Director of the Oncology Center of Excellence and Supervisory Associate Director for Solid Tumor Oncology in CDER.

DR. LARKINS: Erin Larkins, Acting Division Director for Division of Oncology 2.

DR. GOULART: Bernard Goulart, Medical Officer, Division of Oncology 2, FDA.

DR. FORD: Shabnam Ford, Senior Mathematical Statistician, DBV.

DR. MEHTA: Gautam Mehta, Associate Director for Oncology Clinical Policy in the Oncology Center of Excellence, FDA.

MR. MITCHELL: I'm David Mitchell. I am the President of Patients for Affordable Drugs. I'm the consumer representative for this meeting, and I want to thank the FDA for allowing me to participate virtually because I'm on the downside of COVID right now and still contagious.

DR. MADAN: Ravi Madan, Medical Oncologist, National Cancer Institute.

DR. CONAWAY: Mark Conaway, biostatistics, University of Virginia.

DR. STEVENSON: Takyiah Stevenson, FDA Designated Federal Officer.

DR. SPRATT: Dr. Daniel Spratt, radiation oncologist at UH Seidman Cancer Center and Case Western Reserve.

DR. KUNZ: Pamela Kunz, GI medical oncologist, Yale Cancer Center.

MR. PANTELAS: Jim Pantelas, patient advocate and lung cancer survivor, Michigan.

DR. ADVANI: Ranjana Advani, hematological malignancy, Stanford.

DR. LIEU: Chris Lieu, GI medical oncology, University of Colorado.

DR. ROSKO: Ashley Rosko, Division of Hematology, The Ohio State University.

DR. GHAFOOR: Azam Ghafoor, medical oncologist at Thoracic Oncology, NCI.

DR. VAN BERKEL: Good morning. I'm Victor van Berkel. I'm a thoracic surgeon at the University of Louisville.

DR. FRENKL: Good morning. Tara Frenkl. I'm the industry rep. I'm the Head of Global

Medical Strategy and Integrated Evidence Generation at Bayer Pharmaceuticals.

DR. SPRATT: Thank you.

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

In the spirit of the Federal Advisory Committee Act and the Government in their Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the

media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you.

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

Conflict of Interest Statement

DR. STEVENSON: Thank you.

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

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

and to the public.

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

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These

interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussion of a supplemental biologics license application, sBLA, 761069/S-043, for Imfinzi, durvalumab, injection, submitted by AstraZeneca UK Limited. The proposed indication, use, is Imfinzi in combination with platinum-containing chemotherapy as neoadjuvant treatment followed by Imfinzi as monotherapy after surgery, for the treatment of adult patients with resectable, tumors greater than or equal to 4 centimeters and/or node positive non-small cell lung cancer, NSCLC, and no known epidermal growth factor receptor mutations or anaplastic lymphoma kinase rearrangements.

This is a particular matters topic during which specific matters related to AstraZeneca's sBLA will be discussed. The committee will also be asked to discuss whether drug's sponsor should be required to adequately justify treatment of

patients both before and after surgery for resectable NSCLC prior to an approval that would include both neoadjuvant and adjuvant therapy. This is a particular matters topic during which general issues will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product or topic at issue.

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

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

Thank you. I'll hand it back to the Chair.

DR. SPRATT: Thank you.

We will now proceed with the FDA opening remarks, starting with Dr. Erin Larkins.

FDA Opening Remarks - Erin Larkins

DR. LARKINS: Good morning. My name is Dr. Erin Larkins. I'm a medical oncologist and the Acting Director for the Division of Oncology 2. We will be discussing two topics today, the results of the AEGEAN trial and the issue of contribution of

treatment phase in perioperative trials. I will begin by providing an overview of the topics for discussion at today's advisory committee meeting.

To set the stage for today's meeting, it is necessary to describe the various designs of trials, which have been conducted to assess anti-PD-L1 antibodies, hereafter referred to as immune checkpoint inhibitors, or ICIs, as part of the treatment approach for early-stage, non-small cell lung cancer.

There have been trials investigating ICIs given only prior to surgery, termed a neoadjuvant-only treatment approach; trials investigating ICI given only after surgery, an adjuvant-only approach; and trials investigating ICI given in both neoadjuvant and adjuvant phases of treatment. The main focus of today's discussion relates to trials investigating ICI given both before and after surgery, which we will refer to as the neoadjuvant and adjuvant phases of therapy. In the context of FDA's presentation, we will be using the term "perioperative" for regimens incorporating

a new therapy into both the neoadjuvant and adjuvant phases of therapy.

Today, we will be discussing two related topics, a specific marketing application intended to support a perioperative ICI treatment approach based on the results of the AEGEAN trial, as well as design considerations for future trials intended to support perioperative treatment approaches. The overarching issue tying these topics together is the inability of 2-arm trial designs to address the contribution of each phase of therapy in a perioperative treatment regimen, resulting in the potential for overtreatment.

In a 2-arm trial, the relative contribution of each phase, the neoadjuvant phase and adjuvant phase, cannot be established, making it unclear if patients need both phases of therapy. In the past, FDA has granted approvals to perioperative ICI regimens based on 2-arm trial designs, one in breast cancer and one in non-small cell lung cancer; however, emerging data in non-small cell lung cancer has heightened uncertainty around the

need for both phases of treatment, leading to the potential for overtreatment with exposure to avoidable toxicity and increased patient burden.

This emerging data, as well as proposals for 2-arm trial designs for new add-on perioperative regimens, has necessitated this open public discussion on the need to better establish the contribution of each phase to the treatment effect of perioperative regimens.

Currently approved treatment options for resectable non-small cell lung cancer incorporating ICI include two using ICI in the adjuvant phase only; one with ICI given in the neoadjuvant phase only; and one perioperative regimen with ICI administered in both the neoadjuvant and adjuvant phases of treatment.

The adjuvant-only and neoadjuvant-only approvals were based on event-free survival with statistical significance for overall survival not yet demonstrated in these trials. At the time of approval of pembrolizumab for use as a perioperative neoadjuvant and adjuvant regimen, the

KEYNOTE-671 trial had demonstrated a statistically significant improvement in both event-free survival and overall survival.

This next slide shows the available data for approved treatment options, AEGEAN, and publicly available results for another multiregional perioperative trial, CheckMate-77T. While we acknowledge that cross-trial comparisons limit the ability to draw definitive conclusions from this data and are particularly problematic for comparisons between adjuvant-only regimens and those incorporating ICI in the neoadjuvant phase, the observation of similar treatment effect sizes across trials raises concerns for the possibility of overtreatment when using a regimen approach incorporating ICI in both phases of treatment. With this background, I will now provide a high-level overview of the AEGEAN study design and results.

AEGEAN is a 2-arm trial comparing neoadjuvant durvalumab and chemotherapy followed by surgery and one year of adjuvant durvalumab to

neoadjuvant chemotherapy followed by surgery and placebo. The primary endpoints are pathologic complete response and event-free survival, with overall survival one of the key secondary endpoints. Additional details regarding the overall trial design and the statistical analysis plan will be presented by the applicant and reviewed during the upcoming FDA presentation.

At the time the AEGEAN trial was initially proposed, FDA raised concerns regarding the inability of a 2-arm trial design to assess the contribution of each phase of therapy to the overall treatment effect of the perioperative regimen and recommended that an adaptive or factorial study design be considered. FDA provided similar advice across development programs proposing such 2-arm trials. Despite this advice, the applicant opted to proceed with a 2-arm trial.

At the first interim analysis of event-free survival, AEGEAN demonstrated a statistically significant and clinically meaningful improvement in event-free survival with a hazard ratio of 0.68,

favoring the durvalumab arm. Median event-free survival was not reached in the durvalumab arm with a lower bound of the 95 percent confidence interval of 31.9 months. In the control arm, the median event-free survival was 25.9 months with a confidence interval of 18.9 months to not reached. In the Kaplan-Meier plot for event-free survival, the curves begin to separate at 3 months and remained separated, favoring the durvalumab arm. In the statistical testing hierarchy for AEGEAN, testing of disease-free survival preceded testing of overall survival.

At the time of the first interim analysis of event-free survival, the results for disease-free survival were not statistically significant, precluding formal testing of overall survival. At the prespecified second interim analysis for AEGEAN, disease-free survival had still not reached statistical significance. While overall survival could not be formally tested, a descriptive analysis at interim analysis 2 showed a hazard ratio of 0.89 with an upper limit of the 95 percent

confidence interval of 1.14.

We acknowledge that the AEGEAN trial met its primary endpoint and demonstrated a statistically significant and clinically meaningful improvement in event-free survival. In general, event-free survival is considered an acceptable endpoint to support approval in the disease setting of early-stage resectable non-small cell lung cancer, with the ability to support approval dependent on the magnitude of effect, the toxicity profile, and reassurance of no detrimental effect on overall survival.

In the current case, the endpoint is not the issue. The major issue is the inability to assess the contribution of the individual phases of treatment to the observed treatment effect, with heightened concern for this issue given the accumulating data in the non-small cell lung cancer space. As communicated by FDA to the sponsor prior to initiation of the trial, the AEGEAN trial as designed does not allow for determination of whether it is truly necessary to administer

durvalumab in both the neoadjuvant treatment phase and for an additional one year after surgery in order to achieve the observed improvement in event-free survival.

Even if a statistically significant improvement in overall survival is eventually demonstrated in the AEGEAN trial, the inability to demonstrate contribution of phase would still be problematic. While demonstration of an overall survival benefit might seem to mitigate the deficiency in trial design, it does not address the core issue of whether both phases of therapy are necessary to achieve the observed benefit. It can provide reassurance that treatment is not resulting in a number of deaths due to toxicity that exceeds the number of deaths in the control arm, but it does not capture long-term toxicities or patient burden and leaves open the question of potentially exposing patients to unnecessary therapy.

As discussed at the beginning of this presentation, there's accumulating data revealing similar effects across trials for perioperative

versus neoadjuvant-only or adjuvant-only regimens that raises concerns for the possibility of overtreatment when using a perioperative regimen approach incorporating ICI in both phases of treatment.

In addition, at the end of June, the applicant released a statement regarding the high-level results from a large multicenter trial of adjuvant durvalumab for patients with resected non-small cell lung cancer conducted by the Canadian Cancer Trials Group, Study BR.31. The trial did not achieve statistical significance for the primary endpoint of disease-free survival in patients whose tumors expressed PD-L1 on 25 percent or more tumor cells.

While this does not rule out the possibility that adjuvant durvalumab may provide additional benefit when used after neoadjuvant durvalumab and chemotherapy, the results of Study BR.31 do add to the uncertainty regarding the contribution of adjuvant durvalumab to the treatment effect observed in AEGEAN.

In the upcoming presentations, you will hear about ongoing efforts to conduct trials to address questions related to contribution of phase. These cooperative group trials are very important and will provide valuable information to help clinicians determine how to best incorporate ICIs into the treatment of resectable non-small cell lung cancer; however, these trials are not designed to answer the question of contribution of phase for each phase of treatment in all patients eligible to receive perioperative therapy. Additionally, these trials will take many years to conduct and read out, and it is possible that the field may have moved on and the treatment landscape will have evolved by the time these results are available.

This brings us to the second topic for discussion at today's advisory committee meeting, design of future trials in this setting. There are now several FDA-approved options incorporating ICI into the treatment of resectable non-small cell lung cancer, and there is increasing interest in adding new therapies onto these approved

treatments.

For new add-on treatments there are contexts in which a 2-arm trial design would be appropriate. This would include studies adding a new therapy to only one phase of treatment, adding the new agent to either the neoadjuvant phase or the adjuvant phase of therapy. However, adding a new therapy to both phases of treatment will only perpetuate the problem we're discussing today, and given an expected increase in toxicity with add-on regimens, we believe it is even more important to move away from 2-arm trial designs when proposing to add a new therapy to both the neoadjuvant and adjuvant phases of treatment. This issue is relevant now, as we have seen proposals for 2-arm trials adding a new therapy to a perioperative ICI backbone in both the neoadjuvant and adjuvant phases of treatment.

As we've discussed, there is uncertainty regarding whether the use of ICI in both phases of therapy is necessary to achieve the observed clinical benefit. Even if one considers a standard-of-care backbone incorporating ICI in both

the neoadjuvant and adjuvant phases of therapy appropriate, a 2-arm trial design incorporating a new therapy into both phases of treatment will only add to the uncertainty and the potential for overtreatment. As treatment regimens are intensified with the addition of new agents or new mechanisms of action added to anti-PD-L1 therapy, this can be expected to result in additional toxicity.

Letting such 2-arm trials move forward will further perpetuate the uncertainty regarding contribution of treatment phase and the potential for overtreatment. The expectation of additional toxicity with intensification of therapy makes it even more important to have evidence that the additional toxicity and burden of new therapy to each phase of treatment is necessary to achieve benefit. Given this, we feel it is important to discuss alternative trial designs which will allow for some within-trial assessment of the contribution of each phase of therapy to the treatment effect. While we acknowledge that this

will necessitate larger trials, we believe such trials are feasible, as will be discussed in FDA's main presentation.

As shown here, a 4-arm trial design would provide the most rigorous characterization of contribution of phase. A 4-arm trial would allow for separate assessments at the investigational therapy when given as neoadjuvant therapy only, adjuvant therapy only, and as a perioperative regimen. We acknowledge that, depending on the expected effect size, a 4-arm design may require a larger sample size and may not be practical to conduct.

There are several reasons why the biggest concern for overtreatment in a perioperative ICI-containing regimen may be the prolonged treatment in the adjuvant phase; in other words, whether the treatment effect is driven by the neoadjuvant phase with little additional efficacy derived from the adjuvant phase. As such, one alternative approach could be to consider a 3-arm trial design incorporating experimental arms

assessing the investigational therapy given only in the neoadjuvant phase and as a perioperative regimen.

With removal of the adjuvant-only investigational add-on arm, uncertainty will remain regarding the relative contribution of the neoadjuvant phase of therapy to the effect of the perioperative regimen, but within-trial data on the contribution of the adjuvant phase will be obtained.

While it is tempting to throw up our hands and say that conducting multiarm trials is too burdensome, the risk of overtreatment will only be compounded as new treatments are being added on to a standard-of-care backbone. Given the expectation of additional toxicity with intensification of treatment, it becomes even more important to assess what each phase of therapy is contributing to the overall treatment effect. Continued use of 2-arm trial designs will further exacerbate the risk of overtreatment. We believe that to best serve patients and the oncology community, more

thoughtful trial designs are necessary. We look forward to the advisory committee's discussion on how to approach future designs in this development space.

There are two topics we are asking the committee to discuss today. The first is related to how to approach the data already in hand, the results of the AEGEAN trial. The first topic for the committee's consideration is, in light of the uncertainty around the need for both phases of treatment, discuss whether an additional trial should be conducted to clarify the contribution of treatment phase for the durvalumab perioperative regimen prior to approval.

The second discussion topic and question for the committee is how to move forward with future trial designs in this space when proposing to assess a new therapy in both phases of a perioperative regimen; specifically, should FDA require that new trial design proposals for perioperative regimens for resectable non-small cell lung cancer include adequate within-trial

assessment of contribution of treatment phase?

Thank you for your time. I'm going to turn it back over to the chair.

DR. SPRATT: Thank you, Dr. Larkins.

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

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

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

relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the presentations from AstraZeneca UK Limited.

Applicant Presentation - Leora Horn

DR. HORN: Members of the advisory committee, FDA, and guests, good morning. My name is Dr. Leora Horn, and I'm a thoracic medical oncologist from Vanderbilt University. I joined AstraZeneca four years ago, and I'm currently the Vice President and Head of Clinical Development Late Oncology and the Global Clinical Strategy Head for Lung Cancer. I'm pleased to be here today to introduce the AEGEAN study of durvalumab in resectable non-small cell lung cancer.

Durvalumab, also known as Imfinzi, is a well-established, anti-PD-L1 monoclonal antibody engineered to prevent antibody-dependent cell-mediated cytotoxicity. The proposed indication for AEGEAN regimen is durvalumab in

combination with platinum-containing chemotherapy as neoadjuvant treatment followed by durvalumab as monotherapy after surgery for the treatment of adult patients with resectable non-small cell lung cancer and no known EGFR mutations or ALK rearrangements.

There are multiple ongoing trials with durvalumab and lung cancer in a variety of settings. Currently, durvalumab is approved in over 70 countries in locally advanced and metastatic non-small cell lung cancer, small cell lung cancer, endometrial biliary tract, and hepatocellular carcinoma. The AEGEAN regimen is approved in Switzerland and the United Kingdom.

Today, we are discussing a new indication for durvalumab based on the AEGEAN study. AEGEAN is a large randomized, placebo-controlled study designed to evaluate neoadjuvant and adjuvant durvalumab in patients with resectable non-small cell lung cancer. Patients were randomized to receive neoadjuvant carbo-platinum or cis-platinum doublet in combination with durvalumab or placebo.

Upon completing the neoadjuvant phase, patients proceeded to surgery, followed by 12 months of adjuvant durvalumab or placebo.

AEGEAN met its prespecified dual primary endpoints with a statistically significant improvement in pathologic complete response and event-free survival. The latter is a well-established endpoint in registrational trials in resectable non-small cell lung cancer.

In 2018, when AEGEAN was designed, the optimal trial to determine contribution of phase was not well characterized and has since become a focus with readouts of studies in early-stage disease. Resectable non-small cell lung cancer has a high rate of recurrence and systemic therapy is given for the treatment of micrometastatic disease.

There were important scientific and clinical considerations taken into account when designing a regimen with the greatest potential to benefit patients. First, the transformative overall survival outcomes were seen in metastatic non-small cell lung cancer with 4 cycles of induction

platinum-doublet and immunotherapy, followed by maintenance immunotherapy for up to 2 years such as seen in KEYNOTE-189. Second, the optimal duration of immunotherapy remains unknown. CheckMate-153 compared one year to indefinite immunotherapy and found improved survival with longer duration of treatment. Third, a phase 2 trial with neoadjuvant nivolumab in non-small cell lung cancer suggested that 2 doses was not enough for sustained T-cell activation and maximizing IO responses.

And finally, the PACIFIC study showed us that one year of durvalumab following definitive chemoradiation in unresectable stage III non-small cell lung cancer dramatically improved survival and is the global standard of care; therefore, AEGEAN was designed with induction chemo and immunotherapy that aligned with the standard-of-care chemotherapy followed by up to one year of adjuvant immunotherapy.

AZ engaged with the FDA in 2018, before starting and throughout the AEGEAN study, including at the time of primary readout in 2023. The AEGEAN

design was similar to three other pivotal perioperative studies in non-small cell lung cancer that it started to enroll around the same time. There are currently around 20 ongoing studies with comparable designs in multiple tumor indications, including over 17,000 patients with early-stage disease.

During the course of the study conduct, there have been two approvals in the adjuvant non-small cell lung cancer setting, one neoadjuvant-only and one perioperative approval, KEYNOTE-671, which had a similar trial design that did not isolate contribution of phase. The AEGEAN data met the agency criteria based on the demonstrated benefits on event-free survival, supported by pathologic complete response with no detriment in overall survival.

As with any study, there remains some unanswered questions, including the question of contribution of phase. We are leading the field with planned cooperative group trials that we will share, along with ad hoc analysis from AEGEAN that

may shed some light on this topic.

Our presentation today will cover the standard of care in resectable non-small cell lung cancer at the time AEGEAN was designed and today. Details of primary and key secondary endpoints met by the study to support a favorable benefit-risk profile and how AEGEAN helps address an unmet need for patients with resectable non-small cell lung cancer. We will also discuss considerations for the designs of planned studies to answer some of the questions emerging from the AEGEAN and other perioperative studies.

Thank you, and now I'd like to invite Dr. Marina Garassino from the University of Chicago to discuss the disease background.

Applicant Presentation - Marina Garassino

DR. GARASSINO: Good morning, and thank you, Dr. Horn.

I am Marina Garassino. I am the Director of the Thoracic Program at the University of Chicago. I'm not a paid consultant for the sponsor in this role, but I have previously served as a consultant

for AstraZeneca, and I was previously involved in AstraZeneca trials but not in the AEGEAN trial, and I was on the steering committee of KEYNOTE-671.

Lung cancer is the second most common cancer by incidence and the most lethal, representing a significant public health concern. In the United States, resectable non-small cell lung cancer comprises nearly 50 percent of all diagnosed non-small cell lung cancer cases. As you can see, survival rates decline sharply with stage, and 55 to 83 percent of patients such as those in AEGEAN have died within five years.

In 2018, treatment recommendations were guided by a multidisciplinary team. For patients with resectable disease, the standard of care was 3 to 4 cycles of a platinum-based chemotherapy either before or after the surgery, with a modest 5 percent absolute improvement in survival. For patients with unresectable disease, the standard of care changed with the FDA approval of one year of durvalumab after chemoradiation, based on the results of the PACIFIC trial. This represented the

introduction of immunotherapy as a standard of care into the curative intent setting.

The phase 3 PACIFIC trial randomized patients with unresectable stage III non-small cell lung cancer to receive one year of durvalumab or placebo after definitive chemoradiation. The study demonstrated a significant and meaningful improvement in progression-free survival and overall survival with a tolerable safety profile.

Another major advance was the discovery of the synergistic effect of the combination of chemotherapy and immunotherapy. Several phase 3 trials of immunotherapy and platinum-doublet chemotherapy in first-line metastatic non-small cell lung cancer demonstrated a significant survival benefit. These studies led to FDA approval and remain the standard of care in the first-line metastatic setting.

In this trial, immunotherapy was given with 4 cycles of chemotherapy and empirically continued for 2 years or until progression. Given the results of the metastatic setting, together with

the strong benefit of immunotherapy in a resectable setting, AEGEAN was designed. Patients received 4 cycles of chemotherapy and immunotherapy as in the metastatic setting, followed by surgery and adjuvant immunotherapy.

The goals of the neoadjuvant treatment are to reduce the volume of the tumor before surgery and for early suppression of micrometastatic disease. With neoadjuvant immunotherapy specifically, there is an additional benefit maximizing T-cell activation and recognition while the tumor is still present, and with the addition of the adjuvant immunotherapy, we ensure a consolidation of the antitumor activity, allowing the ongoing suppression and elimination of micrometastatic disease.

Today in 2024, there are multiple options for patients with resectable non-small cell lung cancer. The first is neoadjuvant only given after the surgery; the second is the neoadjuvant only given before the surgery; and the third is the perioperative approach with neoadjuvant followed by

surgery, followed by adjuvant like in AEGEAN in the KEYNOTE-671, which was recently approved by FDA.

It is important to share every option in a multidisciplinary tumor board and to discuss each option with each patient. In the adjuvant setting, there are two large trials, including nearly 2200 patients evaluating immunotherapy after surgery. The primary endpoint in both trials was disease-free survival, which includes recurrence and death. This trial showed a 15 to 20 percent reduction in the risk of a DFS event in all randomized patients.

In the neoadjuvant-only approach, we have one single, small randomized trial, including 358 patients evaluating chemoimmunotherapy for 3 cycles prior to surgery. Unlike the adjuvant trials, the primary endpoint here was event-free survival, which includes progression precluding surgery, as well as recurrence and death. This study showed a 34 percent reduction in the risk of an event-free survival event.

Now we move to the three large perioperative

studies including about 2,000 patients. The primary endpoint is event-free survival for all these trials. It should be noted that KEYNOTE-671 only permitted cisplatin-based chemotherapy, while AEGEAN and CheckMate-77T permitted either cisplatin- or carboplatin-based chemotherapy, which is the preferred platinum in the United States. These studies represent a large body of evidence and demonstrate a 30 to 40 percent reduction in the risk of an event-free survival event consistent across all trials.

Let's move to the quality of life that is crucial for patients' choices. The quality-of-life data which I presented at ASCO from the perioperative KEYNOTE-671 showed that there is no difference between treatment arms over time. In particular, adjuvant immunotherapy does not have a negative impact on the patient's quality of life, and you will see similar quality-of-life results were observed also in the AEGEAN.

To conclude, immunotherapy has transformed outcomes for non-small cell lung cancer patients in

recent years. FDA has approved multiple regimens for patients with metastatic non-small cell lung cancer. The field is moving agents from metastatic to early-stage disease, where patients have their one and only chance for a cure. FDA has approved comparatively fewer regimens in early-stage disease.

Durvalumab is an established standard of care with substantial experience in stage III non-small cell lung cancer. AEGEAN is an important study that adds to the treatment choices for patients with resectable disease with no detriment in patient quality of life. Thank you for your attention, and I would like to invite Dr. Doherty to the podium.

Applicant Presentation - Gary Doherty

DR. DOHERTY: Thank you, Dr. Garassino.

I am Gary Doherty. I'm a medical oncologist and global clinical program lead at AstraZeneca, and it's my pleasure today to present the efficacy outcomes from the AEGEAN study. AEGEAN is an ongoing, double-blind, placebo-controlled, phase 3

study. 802 patients with previously untreated resectable stage II to IIIB non-small cell lung cancer were randomized to one of two arms, either durvalumab and platinum-based chemotherapy given every 3 weeks for 4 cycles, followed by surgery, followed by durvalumab given every 4 weeks for 12 cycles; or placebo and chemotherapy, then surgery, then placebo, according to the same schedule.

Randomization was stratified by disease stage and by PD-L1 expression, and the primary endpoints were pathological complete response, or pCR, using IASLC guidelines, and event-free survival, or EFS, using blinded independent central review, or BICR, per RECIST 1.1. Key secondary endpoints were major pathological response, or MPR, disease-free survival, or DFS, using BICR, and overall survival. Other secondary endpoints included patient-reported outcomes and safety and tolerability.

Here we see the MTP, or multiple testing procedure, with pathological endpoints on the left.

The dual primary endpoint of pCR was tested with 0.5 percent alpha which passed to MPR. Given that both were statistically significant, the rest of the hierarchical MTP, including the dual primary endpoint of EFS, was tested with 5 percent alpha. On the right, we see the study analysis sets. 802 patients were randomized. The safety analysis set comprised all patients who received study treatment. Efficacy analyses were performed in the 740 patients with no known EGFR mutations or ALK gene rearrangements, and this is the modified ITT or mITT population, and patients in this population with no evidence of disease postsurgery comprised the resected population relevant for DFS.

Recruitment started in January 2019 and continued until April 2022, and there have been four DCOs to date in the study. The first was for the pCR interim analysis, where statistical significance was demonstrated for both pCR and MPR. DCO2 was for both the final analysis of pathological outcomes for all patients and the first interim analysis of DFS, at which EFS was

statistically significant.

DCO3 was an ad hoc DCO agreed with the FDA for standard safety as well as updated overall survival data, and DCO4 is the latest DCO with a minimum patient follow-up of around 25 months, from which updated EFS and OS data, and now also DFS data, are available. Safety and tolerability were assessed at each DCO and PROs at DCOs 2 and 4.

Here is a summary of disposition for the mITT population at DCO4. Please note that the denominators for all percentages here are 366 for the durvalumab arm and 374 for the placebo arm. Similar proportions in each arm completed all four planned cycles of neoadjuvant chemotherapy and durvalumab or placebo. Similar proportions completed on-study surgery, and patients should have had surgical resection and a post-operative scan before proceeding to adjuvant treatment.

Around two-thirds of patients commenced adjuvant treatment, with 40 to 45 percent completing all planned adjuvant cycles, and of those who started adjuvant treatment, 69 percent of

patients in the durvalumab arm and 64 percent of patients in the placebo arm completed all planned adjuvant treatment. At DCO4, no patients were continuing on any study treatment, with all patients having completed the required safety follow-up.

Baseline characteristics of patients as shown here are well balanced across study arms and are representative of the target population of patients with resectable non-small cell lung cancer. Likewise, baseline disease characteristics are generally representative of the target population and are well balanced. There is representation of the eligible disease stages with around half of patients having N2 disease. Squamous and non-squamous histologies, as well as PD-L1 subgroups, were equally represented. AEGEAN provided important flexibility in platinum choice with platinum treatments being well balanced. Carboplatin was the platinum base most preferred by investigators in AEGEAN, consistent with U.S. practice.

Outcomes for the primary endpoint of pCR are shown here. On the left, we see the pCR interim analysis, where statistical significance was achieved for the 402 patients in the interim mITT population. Outcomes of the final analysis in the full population were highly consistent, and at the final analysis, pCR was achieved for 4.3 percent of patients in the placebo arm and 17.2 percent of patients in the durvalumab arm. A key secondary endpoint of MPR was also statistically significant, increase from 12.3 percent of patients in the placebo arm to 33.3 in the durvalumab arm. Outcomes were also supported by improvement in the presurgical objective response rate.

At DCO2, the first interim analysis of EFS, the addition of perioperative durvalumab resulted in a statistically significant and clinically meaningful 32 percent reduction in the risk of an EFS event. EFS had a maturity of 32 percent with a median follow-up in censored patients of 12 months. The curve separated at around 3 months with separation widening over time. Median EFS was not

reached for the durvalumab arm versus 25.9 months for the placebo arm. The 1-year landmark EFS was improved from 65 to 73 percent and the 2-year landmark from 52 to 63 percent.

At DCO4, with an additional 18 months of study follow-up from DCO2, the improvement in favor of the durvalumab arm was maintained. The hazard ratio remained consistent with that observed at DCO2 being 0.69 with a maturity of 39 percent. The 2-year landmark was improved with durvalumab from 54 to 65 percent, and the 3-year landmark from 48 to 60 percent.

Shown here from DCO4, improvement in EFS was observed across prespecified subgroups. Improvement was observed regardless of age, sex, race, smoking status, histology, and stage. An improvement was also observed consistently across PD-L1 subgroups and with both cisplatin and carboplatin.

At DC04, the key secondary endpoint of disease-free survival had a maturity of 30 percent. The DFS hazard ratio was 0.66 with 95 percent

confidence intervals ranging from 0.47 to 0.92. And while this endpoint was not formally statistically significant, a clear and clinically meaningful trend in favor of the durvalumab arm was observed. As with EFS, the curve separated early in favor of durvalumab and continued to separate over time. Improvement was also observed in landmark analyses, with improvement at 1 year from 74 to 81 percent and at 2 years from 62 to 75 percent.

Overall survival was not mature at DCO2, with a summary being provided to the FDA to facilitate benefit-risk assessment in the context of statistically significant EFS. At that time, the hazard ratio was 1.02 with wide confidence intervals ranging from 0.75 to 1.39. At DC04, with a maturity of 35 percent, the hazard ratio had improved to 0.89, with a clear and sustained separation in the curves starting from around 20 months. AEGEAN enrolled throughout the COVID-19 pandemic, including when vaccines were unavailable, and a preplanned sensitivity analysis for patients

who died from COVID-19 were censored on their date of death and resulted in a further improvement in the OS hazard ratio from 0.89 to 0.84.

To summarize, AEGEAN is a well-conducted, randomized, placebo-controlled study which met both primary endpoints of pCR and EFS. At the final analysis, the pCR rate in the durvalumab arm was quadruple that of the comparator arm. Improvement in EFS was maintained at the second interim analysis, with a greater than 30 percent reduction in the risk of any EFS events. These improvements were observed across preplanned subgroups and were accompanied by trends for improvements in both DFS and OS. The totality of data from the study support a strong and clinically meaningful benefit from perioperative durvalumab, and the trial continues for longer term efficacy data, including overall survival.

Thank you, and I'd like to invite Dr. Patel to share the safety findings from the study.

Applicant Presentation - Mayur Patel

DR. PATEL: Thank you, Dr. Doherty.

Hello. My name is Mayur Patel, and I'm the Vice President for Patient Safety Oncology. Today, I'll be presenting the clinical safety data for the AEGEAN trial. The safety profile of durvalumab is well characterized based on extensive exposure across multiple tumor types and from the postmarketing setting. The most common adverse drug reactions include rash, pruritis, and pyrexia. The majority are low grade and non-serious. Immune-mediated events associated with durvalumab are managed by withholding treatment, corticosteroids, or endocrine therapy.

Safety data for the perioperative regimen was reviewed in the neoadjuvant, surgical, and adjuvant safety periods as outlined in the study schema. The exposure was adequate to assess safety and tolerability. The median number of treatment cycles in both neoadjuvant and adjuvant periods was similar between treatment arms.

The addition of durvalumab to chemotherapy during the neoadjuvant period did not impact the patient's ability to receive 4 cycles of

chemotherapy or undergo surgery. In the adjuvant period, a similar proportion of patients completed all 12 treatment cycles in both arms. Overall, adverse events, grade 3/grade 4 adverse events, and serious adverse events were generally comparable across arms. The majority of adverse events reported were non-serious and low grade.

Fewer grade 3 or 4 and serious adverse events occurred in the adjuvant period. A higher incidence of adverse events leading to discontinuation was observed during the neoadjuvant period, mostly from known chemotherapy toxicities. Adverse events with fatal outcomes were numerically higher in the durvalumab arm, with most being assessed by investigators as unrelated to treatment. Most fatal events occurred during the surgical period. Importantly, there were few deaths in the adjuvant period.

Adverse events treated with steroids, immunosuppressants, or endocrine therapy were classified as immune-mediated adverse events. While these were observed in a higher incidence in

the durvalumab arm, most were low grade and non-serious. Aside from endocrine events requiring hormone replacement therapy, immune-mediated events had mostly resolved on both arms. The most common adverse events were hematologic and gastrointestinal, consisting with chemotherapy toxicities with frequency and severity similar in both arms. As expected, rash, hypothyroid, and pruritis were higher in the durvalumab arm. These were mostly low grade.

The study was conducted at the height of the global pandemic, and COVID-19 events were mainly low grade across both arms. Serious adverse events mainly reflected hematological chemotherapy toxicities, the underlying disease, and surgical complications. Pneumonia and COVID-19 were among the most frequently reported SAEs in both arms. This was not surprising for lung cancer patients being treated during the pandemic. The majority of serious adverse events were assessed as unrelated. Pneumonitis is a known adverse drug reaction for durvalumab and occurred mostly in the surgical and

adjuvant period.

There were numerically more deaths on the durvalumab arm. The majority of the fatal adverse events were observed in the neoadjuvant and surgical period. The most frequent cause of death on both arms was infection. The most common fatal infections in the durvalumab arm were COVID-19. Six COVID deaths were split across periods, with three occurring within 30 days of surgery. COVID deaths occurred during the peak of the pandemic before vaccines were available. All patients had multiple risk factors for COVID mortality. COVID deaths were assessed as not related to any study treatment.

Four fatal pneumonitis events were reported on the durvalumab arm, three occurred within 22 days of surgery, and one fatal event occurred during the adjuvant period. One fatal myocarditis occurred in the neoadjuvant period. The remaining fatal events occurred in single patients and were associated with comorbidities or the post-surgical complications.

The immune-mediated adverse events were observed at a higher frequency in the durvalumab arm. The most frequent immune-mediated adverse events in both arms were hypothyroid events, dermatologic reactions, and pneumonitis. The majority of immune-mediated events were non-serious, low grade, manageable, and resolved. The majority of the unresolved events in the durvalumab arm were endocrine events requiring hormone replacement therapy.

So, what was the impact of treatment from the patient's perspective? To answer that question, we looked at patient-reported physical function. This is a core patient-reported outcome in oncology as noted in FDA's core patient-reported outcomes in Cancer Clinical Trials Guidance. We used Physical Function Scale from the QLQ-C30 to evaluate the impact of both disease and treatment-related symptoms on patients' ability to perform activities that require physical effort. The data was collected using site-based electronic PROs every 3 weeks during the neoadjuvant period

and every 4 weeks during the adjuvant period.

This plot shows the mean change for physical function by treatment arm over time with neoadjuvant on the left and adjuvant on the right. We observed little difference between arms during the therapy, with no clinically meaningful changes, indicating that adjuvant durvalumab did not have an impact on a range of activities requiring physical effort.

When looking more broadly at overall health-related quality of life measured by Global Health Status Quality of Life Scale, the results were consistent with physical function. It's reassuring to note that adjuvant durvalumab had no clinically meaningful impact on overall health-related quality of life, as well as physical function.

In summary, the AEGEAN regimen demonstrated a manageable safety profile consistent with individual agents and no new safety findings were observed. The majority of immune-mediated adverse events were non-serious, low grade, and manageable.

There was no detrimental impact on patient-reported physical function and global health status quality of life. Thank you, and now I'd like to invite Dr. John Heymach to provide his clinical perspective.

Applicant Presentation - John Heymach

DR. HEYMACH: Thank you, Dr. Patel.

I'm John Heymach, Chair of Thoracic Head and Neck Medical Oncology at MD Anderson Cancer Center. I'm a paid consultant to the sponsor, and I'm a thoracic medical oncologist who's treated lung cancer patients for more than 20 years and served as an investigator on the AEGEAN and many other non-small cell lung cancer trials. Thank you for this opportunity to share my perspective.

I'd like to start off by making four key points to frame the discussion. First, unlike in metastatic disease, in the resectable setting, the goal of treatment is to remain disease free or be cured. In my experience, given that more than 50 percent of patients recur, the majority would select a more intensive treatment if it offered the

possibility of more benefit. Second, physicians and patients prefer having the choice to tailor therapies based on factors such as side effects, comorbidities, biomarkers, and efficacy.

Third, although it has not been definitively determined, data from multiple large randomized trials strongly suggest that neoadjuvant and adjuvant immunotherapy together is more effective than neoadjuvant or adjuvant immunotherapy alone for resectable non-small cell lung cancer.

I'd also note that we rarely, if ever, know the optimal duration or contribution of each component of therapy. For example, in metastatic disease, we still don't know how much benefit maintenance immunotherapy provides or whether two years or indefinite therapy is better. Finally, what we do know is that AEGEAN is a highly effective and safe regimen that builds on our extensive experience with durvalumab in the adjuvant setting for locally advanced disease and provides a choice of cisplatin or carboplatin.

Now, earlier studies have demonstrated that

adjuvant and neoadjuvant chemotherapy offer similar modest improvements in outcomes. The NATCH study directly compared neoadjuvant and adjuvant chemotherapy and found no difference in outcomes, but it did find a marked increase in compliance with systemic therapy when chemotherapy was given in the neoadjuvant setting.

Keep in mind there have been no randomized clinical trials for lung cancer directly comparing neoadjuvant, adjuvant, or perioperative immunotherapy. We do know in murine models that neoadjuvant immunotherapy was more effective than adjuvant immunotherapy, and in the randomized clinical trial, SWOG 18O1, we see that perioperative immunotherapy was superior to adjuvant immunotherapy for resectable melanoma. Since we don't have similar comparisons for lung cancer, we can only compare results across trials, which of course carry limitations.

With these limitations in mind, let's see what's known from the studies of the same therapies in different phases of treatments. First, let's

consider the adjuvant KEYNOTE-091 and the perioperative KEYNOTE-671 studies of pembrolizumab. Keep in mind that adjuvant studies like KEYNOTE-091 select for better prognosis patients because they only randomize patients who've already completed surgery and had an R0 resection and completed adjuvant chemotherapy, and are able to receive further systemic therapy. Typically, only two-thirds of patients with resectable disease go on to adjuvant therapy. Despite this difference, you can see the hazard ratio favors the perioperative regimen.

What about neoadjuvant versus perioperative treatment? Here, we have the smaller neoadjuvant CheckMate-816 study and the perioperative study of 77T, both with nivolumab. The hazard ratio favors the perioperative regimen over neoadjuvant regimen only.

Now, there's a question of whether some patients could be overtreated with the perioperative regimen and uncertainty about which patients are benefiting most from the adjuvant

component. In CheckMate-77T and CheckMate-816, it's clear that even patients that achieved a pathologic complete response have a substantial likelihood of recurring. Furthermore, regardless of whether patients achieved a path CR or not, there appear to be better outcomes in those who received adjuvant nivolumab.

Taking a step back, my perspective is AEGEAN is a large, global, placebo-controlled, randomized trial that met its predefined primary endpoints, with a statistically significant and clinically meaningful improvement in both path CR and EFS and a manageable safety profile. The design of the study was similar to a host of other perioperative studies, including KEYNOTE-671, which was approved without demonstrating contribution of phase. Although similar in design, AEGEAN is distinct from KEYNOTE-671 in that it permitted the use of carboplatin, which is the choice of roughly three-fourths of physicians in these studies.

We now have the perspective of multiple large adjuvant and perioperative studies,

comprising roughly 2,000 patients in each group, and the smaller neoadjuvant CheckMate-816 study of 358 patients. As I noted earlier, the choice of multiple effective regimens is good for both patients and physicians, and while no study has directly compared these approaches, the perioperative regimens appear overall to have more favorable hazard ratios and a larger body of supporting evidence.

Finally, AEGEAN provides broadly similar results to other perioperative regimens, which is particularly clear when you compare the cisplatin group of AEGEAN with KEYNOTE-671, which mandated cisplatin, and here you can see essentially the same hazard ratios of 0.59 and 0.58 between the groups.

So how would I discuss AEGEAN with patients? I'd highlight the efficacy benefit with both cisplatin and carboplatin, which is particularly important in real-world clinical practice, as well as our long-standing experience with adjuvant durvalumab from PACIFIC. In my opinion, for most

patients, undertreatment is a greater risk than overtreatment when the goal of therapy is to prevent recurrence and prolong survival. For all these reasons, I consider AEGEAN to provide an important new option that does not require additional study before approval. I also believe AEGEAN can serve as a foundation for new combination regimens to improve patient outcomes.

So what's the best way of moving forward to increase cure rates as quickly as possible? Given the outcomes of this population, I believe the most important question now is how to tailor novel therapies that again increase the likelihood of cures, such as those being explored in NeoCOAST-2. For the majority of patients, I would not be inclined to recommend a contribution of phase study testing one phase of an established regimen given the availability now of the KEYNOTE-671 regimen.

Importantly, if AEGEAN was designed as a 4-arm study originally, we would not have results for many more years. Mandating every study address contribution of phase would dramatically slow our

ability to develop new regimens and increase cures. In short, while AEGEAN and other perioperative regimens represent a meaningful advance, it's important to remember that the majority of patients today still recur, so we have a long way to go and need to get there as quickly as possible for patients. Thank you, and now I'd like to invite Dr. Horn to return to the podium.

Applicant Presentation - Leora Horn

DR. HORN: Thank you, Dr. Heymach.

Now, I'd like to conclude with a summary of the benefit-risk of the AEGEAN regimen and a brief comment on future study designs. What you've seen today is that AEGEAN has demonstrated a statistically significant improvement in the primary endpoints of event-free survival and pathologic complete response. The benefit was observed across all prespecified groups with a trend towards improvement in overall survival and no detriment in patients' health-reported quality of life outcomes.

The safety profile of durvalumab across

treatment phases was manageable and tolerable with no evidence of additional chemotherapy-related toxicities, no impact on patients' ability to undergo surgery, and immune-mediated AEs that were consistent with the known safety profile of durvalumab. The AEGEAN perioperative regimen has demonstrated a strongly positive benefit-risk profile for patients with resectable non-small cell lung cancer.

Now, AEGEAN was not designed to address the question of contribution of phase; however, we have looked within the study to see what phase-specific data we can find. We conducted an exploratory analysis where we looked at event-free survival outcomes based on adjuvant treatment status. We can see here that there's a two-fold reduction in the risk of an EFS event in patients receiving adjuvant therapy compared to those that did not, but these are exploratory and do not formally answer the question of contribution of phase, so a reasonable question the agency is posing is how to move forward with new designs.

Part of the discussion today is if additional data are needed prior to approval of the AEGEAN regimen. It is the sponsor's position that AEGEAN has already convincingly demonstrated a clinical benefit. Importantly, delivering a study in the United States with neoadjuvant therapy alone is no longer possible with the approval of KEYNOTE-671 and the change treatment landscape. AstraZeneca has partnered with cooperative groups to support practice-informing studies that will answer questions that have emerged with AEGEAN and other perioperative trials.

The ETOP study will be conducted in Europe and compare adjuvant durvalumab to observation after neoadjuvant platinum doublet chemotherapy and durvalumab. The SWOG study will be conducted in the United States and evaluate whether patients with tumors that have a pathologic complete response with neoadjuvant chemotherapy and immunotherapy benefit from additional adjuvant durvalumab. AstraZeneca is a pioneer in increasing our understanding of contribution of phase. We are

also committed to working with the agency to appropriately design new practical patient-centric studies with novel therapeutic regimens.

Now, assuming the perioperative therapy standard of care in resectable non-small cell lung cancer, as we discuss new designs we must consider statistical power, maturity, the magnitude of treatment effect, and improved outcomes for patients, along with feasibility. The example shown here from FDA's briefing document is a 3-arm study with event-free survival as a primary endpoint. This trial could range from 10 to 12 years and require anywhere from 650 to 1,740 patients. We evaluated if the study could sufficiently assess contribution of phase as defined by the 80 percent upper bound confidence interval, excluding a hazard ratio of 1. The power to meet this objective ranges from 44 to 62 percent.

It's worth noting that in future trials, the perioperative and neoadjuvant groups are identical until the start of adjuvant treatment, as not all

patients will undergo surgery or start on adjuvant therapy. If AstraZeneca were to design such a study to meet registrational standards, there remains the risk the contribution of phase would not be adequately characterized with efficacy endpoints such as event-free survival; therefore, could short-term novel surrogate endpoints such as path CR or ctDNA be explored?

As we conclude our presentation, we think it's important to highlight how immunotherapy has dramatically changed the lung cancer treatment landscape in the last decade, improving outcomes for non-small cell lung cancer across disease stages. Perioperative durvalumab demonstrated a favorable benefit-risk profile for patients with resectable non-small cell lung cancer.

AEGEAN was a well-designed and conducted study that met its primary endpoints with a statistically significant improvement in pathologic complete response and event-free survival, with a manageable safety profile and no detriment in patients' health-related quality of life. If

approved, AEGEAN can become an integral part of the treatment armamentarium available to patients.

Additionally, AstraZeneca is committed to address some of the remaining questions in resectable non-small cell lung cancer with new studies anticipated to enroll first subjects later this year. Future studies in resectable non-small cell lung cancer need to consider the drug's mechanism of action, trial feasibility, the treatment landscape, patients' preference, and societal burdens. Thank you for your attention, and we're happy to take your questions.

DR. SPRATT: Thank you so much.

We will now proceed with the FDA's presentation, starting with Dr. Bernardo Goulart.

FDA Presentation - Bernardo Goulart

DR. GOULART: Good morning. I'm Bernardo Goulart, a medical oncologist at the FDA. My presentation will convey FDA's clinical perspective on the AEGEAN trial, followed by general considerations about contribution of treatment phase in perioperative trials for resectable

non-small cell lung cancer. I'd like to acknowledge the FDA review team for the AEGEAN trial.

The presentation starts with a brief overview of the treatment landscape for non-oncogene addicted resectable non-small cell lung cancer. I'll then describe the design and topline results of the AEGEAN trial, including its inability to attribute the benefits of durvalumab to the neoadjuvant or adjuvant phase of a perioperative regimen. Subsequently, I'll discuss the need to demonstrate contribution of drugs to each treatment phase in perioperative trials and will conclude by stating the voting question and topic for discussion.

Lung cancer continues to rank as the first cause of cancer-related deaths in the United States. Non-small cell lung cancer accounts for most of the cases, followed by small-cell lung cancer, and nearly 55 percent of patients present with tumor stages IA to IIIB, which include the resectable cases.

For the 45 percent of patients who present with stage IV disease, surgery is generally not an option, and their prognosis has been historically very poor; and although a fraction of patients with resectable disease do achieve long-term survival, the prognosis of patients with stages I to III is relatively poor as well, with local and distant recurrences accounting for most deaths. Therefore, an unmet need exists for improved neoadjuvant and adjuvant systemic therapies that can decrease distant recurrences, eliminate micrometastatic disease, and improve survival. This presentation focuses on neoadjuvant and adjuvant therapies for resectable lung cancer.

It is in this context that we turn our attention to durvalumab for patients with resectable non-small cell cancer as evaluated in the AEGEAN trial. The proposed indication is for neoadjuvant durvalumab in combination with chemotherapy, followed by surgery, and adjuvant durvalumab in patients with tumors of 4 centimeters or greater or with tumor lymph node involvement,

and whose tumors do not harbor EGFR or ALK gene aberrations.

In the past three years, immune checkpoint inhibitors, or ICIs, have joined chemotherapy as systemic therapies for patients with early-stage resectable lung cancer as evidence emerged showing that ICIs improve long-term outcomes in this setting. In the United States, ICIs have received regulatory approval for two adjuvant indications, one neoadjuvant indication, and one perioperative indication, as shown in this slide. As a reminder, for the purpose of FDA's presentation, the term "perioperative" refers to the inclusion of ICIs in both the neoadjuvant and adjuvant phases of a treatment regimen.

Here, we show the relevant regulatory interactions that occurred during the review of AEGEAN. In a meeting held in November 2018, FDA stated that the design of the AEGEAN trial does not distinguish the effect of neoadjuvant durvalumab with chemotherapy from the effect of adjuvant durvalumab. FDA also recommended a factorial trial

design with or without adaptive design elements to address this issue.

In a subsequent meeting held in May 2023, FDA reiterated the same concerns and requested that the applicant provide a method to assess the contributions of durvalumab given presurgery and postsurgery to the effects of the perioperative regimen. Also, since none of the ICIs were approved for resectable lung cancer at the planning phase of AEGEAN, the choice of neoadjuvant chemotherapy as the control arm was deemed appropriate.

As previously explained today, AEGEAN enrolled patients with good performance status, stages IIA to IIIB resectable disease, and documented PD-L1 expression. The stratification factors were tumor stage and PD-L1 expression. Patients underwent randomization in 1-on-1 ratio between neoadjuvant durvalumab in combination with histology-specific, platinum-based chemotherapy for 4 cycles, followed by surgery, and followed by adjuvant durvalumab, 12 cycles of 4 weeks each or

nearly one year.

The patients assigned to the control arm received neoadjuvant platinum-based chemotherapy and placebo for 4 cycles followed by surgery, and then adjuvant placebo for the same duration as in the experimental arm. In a protocol amendment, the applicant modified eligibility criteria mid trial to require documentation of negative tests for EGFR and ALK gene aberrations. This led to a modified ITT population comprising 740 patients, which is the focus of today's presentation.

The dual primary endpoints consisted of pathologic complete response or pCR and event-free survival, or EFS, by blinded independent central review. Key secondary endpoints included major pathologic response, disease-free survival, or DFS, and overall survival or OS. FDA considers EFS an acceptable efficacy endpoint for approval in this setting, assuming no detrimental effects on overall survival and a favorable benefit-risk profile.

Here, we show the hierarchical testing procedure implemented in the AEGEAN trial. The

initial two-sided alpha was split between the two primary endpoints with an alpha of 0.005 allocated to pCR and 0.045 allocated to EFS. Testing for the DFS would take place only if EFS was statistically significant, and testing for OS would take place only if both EFS and DFS were statistically significant.

In the first interim analysis of pCR, the trial met this primary endpoint by showing a 13 percent absolute difference in pCR rate favoring the durvalumab arm. pCR rate was 18 percent in the durvalumab arm compared with 5 percent in the control arm, a difference that was statistically significant, and the results of the final analysis for pCR were consistent with this interim analysis.

In the first interim analysis of EFS, the trial also met this primary endpoint by showing an EFS hazard ratio of 0.68 and a confidence interval of 0.53 to 0.88 favoring the durvalumab arm, a result that was statistically significant. Median EFS was not reached in the durvalumab arm with a lower bound of confidence interval of 31.9 months,

and the median EFS was 25.9 months with a confidence interval of 18.9 months in the lower bound in the control arm. No question, AEGEAN is therefore a positive trial. It met two of the dual primary endpoints. This is not the point of today's discussion.

Here, we show the Kaplan-Meier plot for EFS. The curves seem to separate at 3 months and remain separated for the rest of the trial favoring the durvalumab arm. Here, we show the results of the second interim analysis. EFS hazard ratio of 0.66, confidence interval of 0.47 to 0.93, which was not statistically significant. The median DFS was not reached in either arm, and given that DFS was not statistically significant, the present analysis of OS is descriptive.

The OS hazard ratio was 0.89 with a confidence interval of 0.70 to 1.14. Median overall survival was not reached in the durvalumab arm, but in the control arm, the median overall survival was 53.2 months with a lower bound of confidence interval of 44.3 months.

Here, we show the Kaplan-Meier plot for overall survival at the time of the second interim analysis. The OS curves seem to separate at approximately 20 months and remain separated. The overall results of overall survival do not suggest a detrimental effect of durvalumab on survival.

This table tries to quantify the potential safety concerns with the adjuvant phase by showing the incidence of immune-related events developed doing adjuvant treatment with durvalumab. As you can see, a total of 31 percent of patients developed immune-related adverse events with 5 percent of patients discontinuing or interrupting durvalumab due to these events. The result here suggests that immune-related toxicities developed during the adjuvant therapy of durvalumab are not necessarily trivial to patients.

We also call the attention to the 9 percent of patients who had unresolved immune-related events at the end of the study treatment. These include rare instances of ongoing and potentially bothersome or concerning events such as rash,

diarrhea, musculoskeletal pain, adrenal insufficiency, and pneumonitis. We note the possibility of other immune-related events with the potential for long-term consequences to patients such as nephritis and diabetes mellitus, and although not common, lasting immune-related adverse events can negatively impact the quality of life due to their persistence in a population that may achieve a cure of lung cancer.

To summarize AEGEAN, the trial demonstrated a statistically significant and clinically meaningful improvement in EFS favoring perioperative durvalumab. At present, the analysis of DFS is not statistically significant, precluding formal testing of overall survival. The descriptive analysis of overall survival does not suggest a detrimental effect.

The safety analysis revealed a risk profile that is consistent with the described toxicities of platinum-based chemotherapy and ICIs, with the caveat that 9 percent of patients who received adjuvant durvalumab, had unresolved immune-related

events at the end of study treatment that could potentially impact quality of life.

The AEGEAN results are straightforward in the sense that had this trial been designed as either a neoadjuvant-only trial or an adjuvant-only trial, contribution of treatment phase would not have been an issue and would not have required a discussion at today's ODAC meeting.

The real reason why we're here today and the main reason of the AEGEAN trial is the trial's inability to distinguish the effect of durvalumab given the neoadjuvant phase from the effect of durvalumab given the adjuvant phase of a perioperative regimen. As we will elaborate further, this inability to assess durvalumab's contribution to each treatment phase raises a concern for potential patient overtreatment and avoidable toxicities, which include clinical and time toxicities.

AEGEAN follows a 2-arm trial design as described in this slide. The design entails the use of ICIs in both the neoadjuvant and adjuvant

phases in the experimental arm, whereas the control arm does not include ICIs in any phase. By design, even if the trial demonstrates a benefit for the perioperative regimen, it will not allow us to determine if patients require both the neoadjuvant and adjuvant phases to benefit. If, for example, the benefit is derived entirely from the neoadjuvant chemoimmunotherapy phase, the adjuvant immunotherapy would expose patients to unnecessary toxicities and prolong the therapy for one year.

This trial should ideally provide evidence of the incremental benefit of the perioperative regimen over ICIs given in each treatment phase, and as a side note, the lack of assessment of contribution of treatment phase is a pervasive limitation that applies to other completed or ongoing perioperative trials of ICIs in lung and other tumor types.

As Dr. Larkins previously mentioned, in formal meetings held during the planning and conduct of perioperative trials AEGEAN included, the FDA notified sponsor that the 2-arm design

would not address the contribution of ICIs when given in the neoadjuvant and adjuvant phases of a perioperative regimen. The FDA also recommended multiarm or factorial trial designs for the assessment or contribution of treatment phases, and despite FDA's recommendations, the sponsors have opted consistently to proceed with 2-arm trials, leaving contribution of treatment phase unaddressed.

In the lack of within-trial comparisons of treatment phases, FDA has had no choice but to resort to cross-trial comparisons to infer the contribution of the neoadjuvant and adjuvant phases to the effects of the perioperative regimen despite substantive limitations of such methodological approach.

The next slides will place the efficacy of these perioperative regimens in context with the efficacy results observed in neoadjuvant and adjuvant trials of ICIs in resectable lung cancer as an attempt to establish the contribution of each treatment phase to the effects of the perioperative

ICI-based regimens.

As we have seen in this table, the efficacy data from pivotal trials do not indicate a clear superiority of perioperative regimens over neoadjuvant chemoimmunotherapy or adjuvant immunotherapy based on similar hazard ratios for EFS or DFS as observed across the trials. Again, despite the limitations of cross-trial comparisons, the data indicate the need for stronger evidence to support the benefit of perioperative regimens. As we pointed out earlier, this ideal evidence should have derived from multiarm or factorial trials comparing the neoadjuvant and adjuvant phases to a perioperative regimen.

FDA is particularly concerned about the adjuvant component of perioperative regimens given its longer duration and uncertain advantage over 4 cycles of neoadjuvant chemoimmunotherapy. FDA's concern seems justified based on the applicant's recent press release from June 2024 regarding the adjuvant-only durvalumab trial known as the BR.31 trial. This large trial randomized 1415

patients in a 2 to 1 ratio to receive adjuvant durvalumab versus placebo for one year following resection and optional adjuvant chemotherapy.

The trial did not meet its primary endpoint of DFS in patients whose tumors have PD-L1 expression of 25 percent or greater. The preliminary results from BR.31 do not solve the ongoing uncertainty about potential benefits of adjuvant ICIs after neoadjuvant chemoimmunotherapy. In addition to the uncertainty of an efficacy benefit of the adjuvant phase, greater toxicity may also represent a concern for adjuvant ICIs compared with neoadjuvant ICIs. This meta-analysis of 28 randomized trials evaluated the incidence of severe toxicities of ICIs in the neoadjuvant and adjuvant settings for patients with solid tumors.

For transparency, the FDA did not conduct or formally review this analysis. The odds ratio for grade 3 to 4 toxicities were numerically higher in the adjuvant trials compared with the neoadjuvant trials, and so were the odds ratios for fatal or grade 5 toxicities. These results were consistent

for trials with shorter or longer duration of follow-up.

One limitation is that the analysis of fatal events did not include 6 neoadjuvant trials and did not include 5 adjuvant trials due to the lack of any toxic deaths observed in these trials, which could have biased the estimation of odds ratios; but despite these limitations, the study indicates that the use of adjuvant ICIs may be associated with higher incidence of severe toxicities than use of neoadjuvant ICIs, and thus, while it is unclear whether the adjuvant phase is necessary to achieve efficacy in a perioperative regimen, there is little doubt that the additional year of ICI is likely to be associated with toxicity and burden that may not be needed.

The applicant proposes a path to demonstrate contribution of treatment phase in the postmarketing setting by collaborating with cooperative groups to design trials that address this issue. PROSPECT-LUNG is an example of a 2-arm trial comparing treatment phases. The trial

randomizes patients to upfront surgery followed by adjuvant immunotherapy versus a perioperative approach, neoadjuvant chemoimmunotherapy, surgery, adjuvant immunotherapy. The trial, however, does not include a third arm of neoadjuvant chemoimmunotherapy followed by surgery, and therefore, it does not assess the contribution of the adjuvant immunotherapy, which arguably is the treatment phase that needs further evidence to support a perioperative regimen. In addition, the trial takes years to complete, and the treatment landscape may have evolved by the time results become available, leading to difficulties in the interpretation of the efficacy data.

Another example is one of applicant's funded trials, CLEAR-INSIGHT. Here, patients who achieve pCR after neoadjuvant chemoimmunotherapy and surgery enter the SWOG portion of the trial to undergo randomization between adjuvant durvalumab versus observation. Although this trial may determine if patients can omit adjuvant immunotherapy, the results will only apply to the

nearly 25 percent of patients who achieve pCR from neoadjuvant therapy. Second, like PROSPECT-LUNG, this trial will also take years to complete, and the treatment landscape may have evolved by the time of study completion.

Finally, the applicant is also funding ADOPT-Lung, a trial to be conducted by the ETOP cooperative group. Here, after neoadjuvant chemoimmunotherapy and surgery, patients with R0 or R1 resections undergo randomization to receive adjuvant durvalumab for approximately one year in the experimental arms versus observation in the control arm. The primary endpoint is EFS in patients without a pCR, and although the design of ADOPT-Lung addresses the contribution of adjuvant therapy to the perioperative regimen, it also presents some important limitations.

First, the relatively small sample size raises concerns for an underpowered study. Second, the estimated time to trial completion is March 2030. With such long timelines, again, the treatment landscape may have evolved by the end of

the trial, and these examples highlight the challenges of conducting postmarketing cooperative group trials to address contribution of treatment phase and underscore the importance of properly assessing contribution treatment phase in the premarketing setting.

Given the concerns presented regarding the AEGEAN trial, I'd like to pose the following discussion topic for the advisory committee one more time. In light of the uncertainty around the need for both phases of treatment, discuss whether an additional trial should be conducted to clarify the contribution of treatment phase for the durvalumab perioperative regimen prior to approval.

We'll now transition to the second part of this presentation. Here, the purpose is to discuss alternatives for drug development in resectable lung cancer that account for contribution of treatment phase. This part of the presentation, we specifically consider trial designs that address not only the efficacy but contribution to treatment phase of novel drugs when added to standard-of-care

regimens in resectable non-small cell lung cancer.

At the FDA, we are aware of proposed trials evaluating novel drugs in resectable disease that follow the design we show here. Companies are proposing 2-arm trials that often include a perioperative chemotherapy and immunotherapy regimen as the control arm and as the backbone to the experimental arm despite the ongoing uncertainty as to patients needing both neoadjuvant chemoimmunotherapy and adjuvant immunotherapy.

Here, the experimental arm consists of adding a novel drug X to both the neoadjuvant and adjuvant phases on top of the perioperative regimen, which again is uncertain. The design exacerbates concerns for overtreatment and toxicities due to intensification of therapy by adding drug X to a multidrug regimen and by not assessing the contribution of drug X to the treatment phase. Moving forward, drug development plans in this setting should assess the efficacy of adding novel drugs and their contribution of treatment phase. The next slides will discuss drug

development strategies that may assess efficacy while accounting for contribution of treatment phase.

As Dr. Larkins presented previously, 2-arm designs of add-on drugs may be appropriate in certain contexts. One such context is adding the new drug to the standard of care in only one phase of treatment as either adjuvant or neoadjuvant therapy only and compare this regimen against a standard-of-care control arm. Given the concerns for lack of assessment of contribution to treatment phase, FDA considers it inappropriate to design 2-arm trials to evaluate the novel drug given as a perioperative regimen against a standard control arm that does not include the novel drug in any treatment phase.

I will now pause and invite my colleague, Dr. Shabnam Ford, to present on the statistical considerations for trial designs involving add-on novel drugs for resectable non-small cell lung cancer.

Dr. Shabnam?

FDA Presentation - Shabnam Ford

DR. FORD: Thank you, Dr. Goulart.

Good morning. My name is Shabnam Ford. I am the Primary Statistical Reviewer for this application. As you heard in Dr. Goulart's presentation, it is critical that future study designs in this setting not only provide evidence of efficacy of the perioperative regimen but also generate sufficient data to adequately assess contribution of the phases of the regimen. Various trial design options are available to accomplish this within a single trial, including 3- and 4-arm trials, which will be the focus of the next set of slides.

A full factorial design with four treatment arms is shown in this schema. This design allows for assessing the contributions of the phases by facilitating comparison of the addition of a new drug to the entire perioperative regimen, the neoadjuvant-only regimen, and the adjuvant-only regimen. In addition, it enables the assessment of the efficacy of the new drug to each experimental

arm. While this design provides a complete evaluation of the contribution of the phases, which may be necessary in some cases, it requires a larger sample size.

A practical alternative to the 4-arm factorial design is to utilize a 3-arm design. As Dr. Goulart discussed, the impact of overtreatment is the highest in the adjuvant phase, which is typically given for a year or more. Thus, a reasonable option would be to incorporate a third arm investigating the new drug in the neoadjuvant-only phase. This approach would provide within-trial information and the contribution of the adjuvant treatment while preserving the ability to statistically test a potentially safe and effective addition of a new drug to the only neoadjuvant phase of therapy.

In the next few slides, we will explore the key considerations for a study design and analysis of these multiarm studies. In multiarm trials, FDA recommends formal testing of each experimental arm to the control arm. A variety of approaches can be

used to formally test these comparisons. In addition, comparison of the experimental arm is essential to adequately evaluate the contribution of phase of therapy, and this should be prespecified in the study protocol and a statistical analysis plan.

This approach mitigates risk. For example, if the comparison between the perioperative and neoadjuvant-only arm does not support the contribution of the adjuvant treatment phase, addition of a new drug to the perioperative treatment is unlikely to be granted approval, but if a statistically significant and clinically meaningful treatment effect is observed in the neoadjuvant-only arm compared to the control arm, a new neoadjuvant regimen could be approved.

Sample size in any trial is driven by design assumptions, testing strategies, and study power. While multiarm trials in this setting will require more patients than a 2-arm trial, FDA estimates potential sample sizes under a variety of reasonable assumptions for an EFS endpoint range,

from 650 to 1700 patients in a 3-arm design and from 960 to 2400 in a 4-arm trial design. These sample sizes include formal comparison of each experimental arm to control arm. While comparisons across experimental arms should be dictated by available information and the therapeutic context, these calculations support the feasibility of conducting multiarm studies in this therapeutic setting.

In particular, for a new trial with larger and more clinically meaningful treatment effects, the expected sample size would be similar to previously conducted 2-arm trials in the perioperative setting. Additionally, the final analysis of this trial is expected to be between 7 to 8 years from the enrollment of the first patient with the possibility of the positive interim readout within 5 to 6 years.

Now, I will hand the presentation back to Dr. Goulart.

FDA Presentation - Bernardo Goulart

DR. GOULART: Thank you, Dr. Ford.

To recapitulate, current trial designs preclude the assessment of contribution of effects of ICIs when given in the neoadjuvant and adjuvant phases of a perioperative regimen, raising concerns for patient overtreatment and avoidable toxicities. FDA expresses particular concern about the lack of assessment of the contribution of the adjuvant phase given its longer duration and potential for greater toxicities, as shown before, in the context of uncertain benefits as seen in ICI trials.

The cooperative group trials are attempting to address contribution of treatment phase but the inherent limitations and long timelines of postmarketing studies suggest that this strategy will not fully address the issue. Companies continue to propose 2-arm perioperative trials, including trials of novel drugs added to a perioperative chemoimmunotherapy backbone, exacerbating concerns for overtreatment given the expectation of incremental toxicities.

Alternative trial designs, including, for example, 3-arm trials, may address contribution of

treatment phase to perioperative regimens. Two-arm trials may be acceptable strategies to evaluate the addition of novel drugs to standard-of-care therapies if the new agent is given in neither the neoadjuvant only or the adjuvant phase only. Two-arm trial designs are problematic if they compare a new drug given in both phases to a control arm consisting of standard of care alone.

With all these considerations in mind, we turn the attention to the one discussion topic and the one voting question for today. For the first discussion topic, in light of the uncertainty around the need for both phases of treatment, discuss whether an additional trial should be conducted to clarify the contribution of treatment phase for the durvalumab perioperative regimen prior to approval.

Given the greater understanding of the issue involving contribution of treatment phase, the second question is, should the FDA require that new trial design proposals for perioperative regimens for resectable non-small cell lung cancer include

adequate within-trial assessment of contribution of treatment phase?

I thank you for your attention, and I hand back the meeting to the chair. Thank you.

Clarifying Questions

DR. SPRATT: Thank you.

We will now take clarifying questions to the presenters. When acknowledged, please remember to state your name for the record before you speak and direct your questions to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Are there any clarifying questions for the presenters? I'm going to start with one.

This is for the applicant. Again, this is Dr. Dan Spratt. This ODAC, as we've heard repeatedly, is principally around understanding the

contribution of phase of therapy, so my only question is, when the FDA met in November of 2018, prior to your trial starting in January of 2019, with the request to better understand the contribution of phase, why did you not comply with this request?

I would appreciate a direct answer, and possible things to help could be, is this because of cost? Is this time? Is this to maximize drug exposure? Is this lack of agreement with the FDA that this matters if the trial ultimately is positive? Is this you don't feel it's your responsibility; or is it because other trials didn't do this, so you don't think you need to, or some other reason? Thank you.

DR. HORN: Leora Horne, AstraZeneca. I'm going to start answering the question, and then Karen McCullough from Regulatory will shed some light on our interpretations of the discussions with the agency, and Helen Mann from Biostatistics will come up and discuss some of the sample size considerations that we had.

We've learned a lot about immunotherapy in the last six years. Back in 2018, we were seeing these transformational outcomes with immunotherapy and chemotherapy in metastatic non-small cell lung cancer, as I mentioned previously in my presentation. At the same time, we recognize that two years, or indefinite therapy, in early-stage disease was not appropriate for lung cancer patients.

Our PACIFIC trial had read out, and that included stage III unresectable non-small cell lung cancer patients given definitive chemoradiation therapy, followed by one year of durvalumab. The PACIFIC study had stage III patients, and in the AEGEAN study, actually 72 percent of patients that were enrolled were stage III. Those are the patients that thoracic surgeons were thinking about in terms of neoadjuvant therapy, so one year of therapy seemed an appropriate amount in the adjuvant setting.

We also had Patrick Ford's data from his phase 2 study that suggested 2 cycles of

neoadjuvant nivolumab was not enough for sustained T-cell activation and really maximizing that immune response. We've actually since seen an updated analysis from Patrick's data published last year that showed that the majority of patients treated with those 2 doses of neoadjuvant nivolumab had occurred. So following the science of what we knew about immunotherapy at the time, we determined that the best study was induction chemoimmunotherapy followed by surgery in that one year of maintenance immunotherapy in resectable disease.

I'd like to call on Karen, who will discuss the regulatory discussions we had with the agency at the time.

DR. SPRATT: Thank you. Just to clarify, so the reason, though, that the FDA's recommendation you guys didn't comply with is because you believe that you had sufficient data that neoadjuvant alone with durvalumab would not be effective?

DR. HORN: We did not have any data with durvalumab; we had external data with nivolumab showing that, potentially, you don't get the

sustained T-cell activation. We were seeing some path CRs, but with the immunotherapy, that whole part is inducing the T cells, memory T cells, and really mounting that immune response; and when you see that reduction in T-cell clones, maybe patients are going to progress. And no one really knew how long you should be giving immunotherapy for either resectable disease or, quite frankly, in metastatic.

DR. SPRATT: I'm just going to push once more. So why not add the additional arm as requested so that you could answer the question?

DR. HORN: So we are going to answer that question, looking at the sample sizes that were calculated, and if you're okay with Karen with the regulatory discussions, then we'll come to Helen, because we did look at a sample size.

DR. McCULLOUGH: Karen McCullough, Regulatory Affairs. You have pointed out that in 2018, we met with the agency, and they did indicate at that time that our design, our 2-arm design, wasn't going to isolate the neoadjuvant from the

adjuvant components, and they suggested a factorial or adaptive design. We acknowledged that the study design didn't isolate those components. While it wasn't our understanding at that time that this was a barrier to approval, we did look at what alternate designs would look like.

So what Dr. Horn has just explained to you is that we had evidence that there was some suggestion that neoadjuvant would contribute to the overall effect. There was also some evidence to suggest that adjuvant might contribute to the overall effect. We didn't have any evidence that would suggest that one arm was going to drive the overall effect, and therefore, when we looked at this, we assumed we would need a 4-arm study to address this request. And with that in mind, we decided, as other sponsors decided, that the optimal path forward was a 2-arm design.

Now, I'll have Helen come up, and she can share with you the statistical assumptions.

MS. MANN: Helen Mann, Biostatistics. Can we have slide 2 up, please? You can see at the

top of this table the actual AEGEAN study, where we planned three analyses and had those analyses with an overall size of 740 patients. You can see the timelines for the study. If we draw your attention to the row with the 4 arms included, we can see what the size looked like. If you compare that to the size of the AEGEAN trial with 740 patients, you can see that we would estimate that that trial with the 4 arms would have been just over 2,500 patients, so notably larger than the AEGEAN study was, at 740 patients.

So size is a consideration. The other consideration was around timelines. If you look at our 40 percent maturity analysis, we planned to have that, and the actual readout of that would plan to be May 2023. If we take those and we've taken the AEGEAN assumptions at that time when we were planning in 2018, the 4-arm trial with 40 percent maturity would not be reading out until q3 2027. Thank you.

DR. SPRATT: Thank you so much. I appreciate that. That concludes my questions. So

it would add 2 years approximately for a 3-arm design.

DR. HORN: Correct, and we were aware of the changing treatment landscape and the potential inability to complete the study as perioperative and neo and adjuvant trials were reading out.

DR. SPRATT: Does FDA want to respond?

DR. LARKINS: Yes, please. As a participant in all of the meetings at the time when we were meeting with multiple companies for this, I would like to clarify that we did not request, necessarily, 4-arm trial designs. We discussed at the time that that would be ideal; however, we offered the option of 3-arm trial designs similar to what we've been talking about going forward.

We also had some discussions at the time that formal comparisons statistically powered the way you saw it in their sample size estimations, 80 percent may not be necessary. So I would like to point out that those sample sizes may be an overestimate of what may have been feasible. We at the time discussed that we very strongly felt it

was important to do 3-arm trials. We did not feel at the time that it was something we could put studies on hold for.

DR. PAZDUR: I have a question for AstraZeneca. The Canadian study that was reported as negative, how many patients were in that trial? I believe it was almost 1400; correct?

DR. HORN: Correct.

DR. PAZDUR: That was done in Canada only; correct?

DR. HORN: No, that was a global study.

DR. PAZDUR: It was a global study.

DR. HORN: It was supported by AstraZeneca, but it was run in multiple countries.

DR. PAZDUR: Okay. But adjuvant studies have been large in size. This is not unheard of to have a thousand patients, or even more, in an adjuvant study.

DR. HORN: Correct.

DR. PAZDUR: I just want to clarify that for people that are not familiar with adjuvant studies. We're not talking usually about small studies here,

but many times in the cooperative groups, in breast cancer, et cetera, we've had 1,000-patient studies, plus thousands, and sometimes 2,000 patients, obviously.

DR. SPRATT: Thank you. We're going to move on. The next question is from Dr. van Berkel.

DR. VAN BERKEL: Thank you. I'm Victor van Berkel from the University of Louisville. First, I'd like to thank both AstraZeneca and the FDA for both very thoughtful and thorough presentations. I also have an etiquette question. I have a couple different questions, and I don't know if I'm supposed to ask one and then yield to somebody else, or if I just run through the list of questions that I have.

(No response.)

Sorry. From an etiquette standpoint, I have a couple of different questions.

DR. SPRATT: Just start with one at a time and let them respond, if possible.

DR. VAN BERKEL: Yes, sure. But then do I let other people ask questions or do I go back to

whatever I want?

DR. SPRATT: Maybe you can do two questions. Let's see how long the responses are --

DR. VAN BERKEL: Fair enough.

DR. SPRATT: -- and how relevant they are.

DR. VAN BERKEL: My first question is actually for the FDA. Were similar concerns about the phase issues raised for the KEYNOTE-671 and CheckMate-77T trials?

DR. LARKINS: So CheckMate-77T is currently in-house and under review, so that one we're not able to discuss. The elephant in the room, obviously, is the KEYNOTE-671 trial, which was approved. It was considered. It was discussed heavily among the teams at the time of approval. I will also let our statistician speak briefly about some of the analyses that have been done on other trials in-house to try to assess these things.

I would note that did have an overall survival benefit. As noted, that does not mitigate or doesn't remove the issue of contribution of phase in any way. We still can't parse out where

the benefit is coming from; however, it is fair, we believe, for that to be taken into the risk-benefit consideration, potentially, for an overall risk-benefit of a regimen, so there are some slight differences.

The even bigger issue, though, is that data continued to emerge after that, so the CheckMate-77T read out after that approval. That is one of the only spaces where we have a neoadjuvant-only regimen and a perioperative regimen, so that sort of added; and as the perioperative regimens all read out, we're seeing similar-ish effect sizes, and then comparing them all to the adjuvant and the neoadjuvant, it just all added to raise some concern.

The other issue that drove us to this is that we were beginning to get proposals for add-on designs. So our major concern is continuing to perpetuate this. Regardless of your thoughts on the first part, we see these as separate questions. The data in hand from AEGEAN, we want to hear your opinions on that and where we go with that. A

separate question is where do we go from here? So regardless whether you think it needs more study or not, we don't think that means we have to keep going forward with 2-arm trials necessarily later for future add-ons. So that's really where our focus is.

I don't know if our stats wants to briefly address some of the data that we've tried to look at.

DR. FORD: I invite Dr. Amatya to provide his perspective.

DR. AMATYA: Yes. Thank you. Anup Amatya, statistics. We raised these concerns during our IND phase in review of this trial and in also the NDA phase. As part of the submissions, we get patient-level data submitted to us, so with that, we look at the adjuvant phase, KEYNOTE-091 data and our perioperative 671 data, and tried to do as much as we could with different statistical methodologies to match baseline characteristics of the patients.

What we found is that there were minimal

differences between those who received perioperative therapy and just adjuvant therapy, but there was a positive trending. So at the time, in absence of other trial data, we felt that there may be some support here, but as we see with new data, that support is less and less with emerging data. Thanks.

DR. SPRATT: Just a reminder, can you make sure you say your name before you speak, for the press? Thank you.

DR. VAN BERKEL: I have I guess one more question.

DR. SPRATT: State your name.

DR. VAN BERKEL: Sure. I'm Victor van Berkel still, and this is a question for AstraZeneca, and forgive me if I mess up your names. Both Dr. Garassino and Dr. Heymach discussed the importance about discussing options with patients when it comes to different treatment opportunities. And I guess my question for AstraZeneca, with us not understanding the difference in phase issues, if CheckMate

demonstrated a 34 percent reduction in event-free survival with no adjuvant therapy and AEGEAN had a 31 percent reduction in event-free survival with one year of adjuvant therapy, how would you justify to a patient before giving them an extra year of therapy without an obvious event-free survival benefit?

DR. HORN: Leora Horn, AstraZeneca. I'd like to ask Dr. Garassino to come up and answer that question. She's recently published a paper on this.

DR. GARASSINO: Marina Garassino, University of Chicago. I think this is clearly the key question of the discussion. I think that as a clinician treating lung cancer, we should always think that this is a very lethal disease, so the majority of our patients, unfortunately, die. As a scientist and also as a clinician, I'm not sure that we are in a situation where we can de-escalate trials; and if you can open slide number 2, you can view again the survival rate.

The second is about the toxicity. I want to

be provocative, and the most important toxicity of lung cancer patients is the recurrence. So in my opinion, we should try to --

DR. SPRATT: I'm sorry to interrupt you, but the question that he asked --

DR. GARASSINO: Yes. The question is --

DR. SPRATT: -- if you could address the question he asked.

DR. GARASSINO: -- I address. Sorry.

I talk exactly with the patients, and they say that we don't know if neoadjuvant is superior, inferior, or the same to the perioperative, and I leave it to the patients, their decision, to decide. Second, in the multidisciplinary tumor board, we discuss the clinical conditions for the patients, and for some patients, the adjuvant is not indicated.

DR. HEYMACH: John Heymach, MD Anderson. Since it was raised and was mentioned here, I'll comment as well. We don't formally have the comparison of perioperative to either one. In the case of the 77T study, we've got the CheckMate-816

and the 77T, one being neoadjuvant only and one being perioperative.

Now, just numerically, the hazard ratio is better for 77T than it is for CheckMate-816. There's also a subgroup analysis here. I don't know if we have the subgroup analysis from 77T with and without adjuvant therapy. You could put slide 3 up, but I'll talk about the subgroup analysis.

Subgroup analysis was presented by Dr. Tina Cascone at a plenary session, and what it showed is that patients from 77T who received adjuvant therapy had better outcomes than those who didn't receive adjuvant therapy, similar to what we saw here for the patients with durvalumab who received adjuvant or didn't receive adjuvant therapy from the AEGEAN study.

Now again, we don't have a formal comparison, so we can't say that proves that adjuvant therapy is adding benefit, but we can say the studies that give us the best or the most direct exploratory analysis, we see that perioperative has a better hazard ratio here, and

patients in 77T who received the adjuvant had more benefit than those who didn't receive the adjuvant in those two studies, again, similar to what we're seeing in AEGEAN. In AEGEAN, the subgroup that received adjuvant had more relative benefit than those who didn't receive.

DR. VAN BERKEL: Thank you.

DR. SPRATT: Yes, if FDA wants to respond to that.

DR. LARKINS: Hi. Erin Larkins, FDA. I would like to start by stating that what you're seeing here is part of what has raised our concerns with 2-arm trials. This is why we have been asking for 3-arm trial designs and why we think it's even more important going forward with toxicity because we are relying on cross-trial comparisons.

We had a mini symposium and a public workshop with AACR, and what we heard from lung cancer providers there is the same thing you're hearing here. They are having to go to patients with incomplete information and try to help them figure out what the best treatment option is, and

often it's left up to how individual tumor boards operate. Some like to go right to surgery, some like to do neoadjuvant. It's left up to patients and providers in the community on what they're most comfortable with using. So this is really kind of the gist of the issue of why we're concerned with perpetuating as a problem going forward.

I would like to give our stats colleagues -- after our representative.

DR. PAZDUR: I think we also have to realize that some of these people will be actually cured by their surgery alone, so we should be having a higher standard here for adjuvant and neoadjuvant than we would have for people that are facing no other therapeutic options and are destined to die very soon from their disease.

So here again, I think it's important that we have to realize that there should be a higher standard here when we talk about the body of evidence that we subject people to and their therapy here. Here again, some of these people will not even need any therapy. We don't know who

those people are, and that's unfortunate, but that is an issue here. So we really should have a higher level of evidence that we have before we subject people to these therapies.

DR. SPRATT: I'd like to go on.

DR. LARKINS: I would --

DR. SPRATT: I'd like to go on.

DR. LARKINS: -- like our stats colleagues to address.

DR. SPRATT: I'd like to go on to the next speaker, but thank you.

DR. LARKINS: Okay.

DR. SPRATT: Dr. Lieu?

DR. LIEU: My question was already addressed, thank you.

DR. SPRATT: Okay. Great.

Dr. Rosko?

DR. ROSKO: Ashley Rosko. My question is for the FDA, or Dr. Goulart specifically, regarding slide 33 and slide 34 that were presented. Perhaps this is a bit of a circular discussion, but I'm really trying to get a handle on the current

treatment landscape for patients with stage II-IIIB non-small cell lung cancer in light of the KEYNOTE-671 data.

What would you define, or what would the FDA define, within those lines of therapy as the standard of care in light of specifically the KEYNOTE-671 study, having both perioperative and overall survivor advantages there?

DR. GOULART: Thank you for the question. Bernardo Goulart, FDA. FDA considers standard of care what FDA approves. FDA is not in the place of dictating medical practice; however, FDA will consider the standard of care and the regimens approved based on safety and effectiveness, which would include KEYNOTE-091 and pembrolizumab; neoadjuvant chemotherapy with nivolumab, CheckMate-816; adjuvant atezolizumab, IMPower-010; and KEYNOTE-671. All of these are standard-of-care therapies.

DR. ROSKO: I think my general concern --

DR. SPRATT: Please state your name.

DR. ROSKO: Oh, I'm sorry. Ashley Rosko.

My general concern is just about also the undertreatment of certain patient populations. So I guess if you have clinician decision, and access issues, and patients being treated in the community, I have concerns about that as well. And I know that's the gist of this conversation and how this trial was designed, and limited performance status and good renal function that doesn't necessarily represent a lot of the community in the patients that are suffering with this disease.

So I asked that question just because a lot of times when you're thinking about equipoise for clinical trials, and you're thinking about what is really uncertain in that setting, and you have a study that was published and put out with a survival advantage, it really drives questions; and sometimes having clarity about what the FDA considers to be the standard of care helps drive future decision making, so thank you for your answer.

DR. GOULART: Thank you.

DR. SPRATT: Great.

We'll go to Dr. Ghafoor.

DR. GHAFOOR: Hi. My name is Azam Ghafoor with NCI. I have a couple questions. One's on efficacy and one's on toxicity. The first question I have I think is for Dr. Heymach and is regarding the EFS analysis. Prior trials like the CheckMate and other perioperative trials have looked at EFS compared to pCR and non-pCR. Are you guys able to provide that data today, and whether patients with pCR benefited more with durvalumab?

DR. HORN: You're asking for this data from the AEGEAN study?

DR. GHAFOOR: Yes.

DR. HORN: Yes, we have that data. I'm going to ask Gary Doherty to come up and present that data.

DR. DOHERTY: Thanks for the question. So we have performed analysis of EFS and DFS by pCR status in AEGEAN, and it should be noted that pCR status is, of course, a post-randomization subgroup, so we have to take all of these with caution, and the EFS is very immature, as is the

DFS, in patients with pCR. Patients with pCR, those have likely benefited most from neoadjuvant treatment, but these patients do still experience recurrence, as we see now in multiple studies, including CheckMate-816 and the perioperative studies.

If we could have slide 4 up, please? There are concerns, as Dr. Heymach alluded to, about overtreatment, particularly in patients who have better outcomes. As we can see here, in patients who had a pCR in either arm of the study, disease-free survival numerically improved in patients who were in the durvalumab arm of the study. The hazard ratio between the arms was 0.31. Of note, the maturity here is is very low, 12 percent.

If we could also look at slide 3, please, slide 3 up. This is an analysis that's been repeated across multiple studies. Now, in patients with pCR, the EFS hazard ratio was 0.73. We can see here that patients with pCR do have better outcomes compared with those who don't have pCR,

but the hazard ratio is 0.73 for those with pCR and 0.81, with sustained separation in the larger more mature group. So we do see benefit regardless of pCR status within the study.

DR. SPRATT: Okay. Thank you.

DR. HORN: This is Leora Horn, AstraZeneca. I just want to highlight, as we're showing this data, which probably adds to the FDA's confusion as we're reviewing, the analysis of pCR in the AEGEAN study was done with IASLC staging, with the IASLC recommendations. The CheckMate-816 and 77T studies had a different analysis of pCR, so it's not quite comparing apples to apples when you look at the pCR populations in AEGEAN, which is a more thorough review of lymph nodes and tumor samples compared to 816 and 77T.

DR. GHAFOOR: Okay. Thank you.

This is Azam Ghafoor. I have one more question. Regarding the immune-mediated AEs, the ongoing unresolved, can you comment on the characterization of those, how many patients or what type of hormonal therapy replacement, and what

are they, pan-hypopit or diabetes? Can you clarify on those 38 patients?

DR. HORN: I'd like to call on Dr. Mayur Patel from patient safety to answer that question.

DR. PATEL: Mayur Patel, Patient Safety. If I could have slide up, please? As we noted before, the imAEs were non-serious and low grade and many of them had resolved. When focused on the imAEs that did not resolve, in our briefing document, just to clarify, we had grouped all of the resolving and not resolved together; that's the 29 that you see there. When you look further at just those that were not resolved, as you can see here, those that require hormone replacement therapy are mostly hypothyroid events requiring a thyroid medication and one event of adrenal insufficiency. You can see the other events are quite low in the others and they were all low grade. Thank you.

DR. GHAFOOR: Thank you. I yield back.

DR. SPRATT: Great. Thank you.

We'll move to Dr. Kunz.

DR. KUNZ: Hi. Pamela Kunz, Yale Cancer

Center. I have a question that's also related to toxicity, and I think that certainly the FDA presented data highlighting slide 23 on risk of toxicities for adjuvant ICI versus control, versus neoadjuvant period. AstraZeneca really focused on similarities between quality of life. I think there's certainly a financial incentive for the applicant to provide longer treatment, certainly a year, in the adjuvant setting.

I'd like perhaps both the agency and the applicant to comment a little bit more on this risk of toxicity and also financial toxicity, which was not addressed. Certainly, a longer period of treatment for patients poses risk of lost time at work and additional issues around financial toxicity.

DR. SPRATT: Who would you like to start?

DR. KUNZ: Perhaps the agency.

DR. GOULART: Bernard Goulart, FDA. I would like to first tackle the question about toxicities. Yes, I'd like to remember that the data I presented on the meta-analysis applies to patients with solid

tumors, and these were patients treated in 20 trials that had either neoadjuvant ICIs versus a control or adjuvant ICIs versus a control. Then, I also tried to look at severe toxicities and, yes, severe toxicities were numerically more frequent in patients treated with adjuvant ICIs relative to neoadjuvant ICIs.

The concern the FDA has about this is that given not only the longer duration of adjuvant regimens, this potential for greater toxicities may have an impact in quality of life in that fraction of patients who experience lasting immune-related events. So even though average quality-of-life metrics may not capture this particular concern in the overall trial population, we maintain a position that a fraction of the patients may have a significant detriment in quality of life because of persistent toxicities as supported by that meta-analysis.

Can you remind me what the second part of your question is?

DR. KUNZ: Pam Kunz. Yes, it's around

financial toxicity.

DR. GOULART: Yes, the FDA typically does not comment on financial aspects of cancer care.

DR. KLUETZ: Paul Kluetz, FDA. I just wanted to mention, just to keep in mind as we talk about the next discussion topic, the IO-only monotherapy safety is well known, I think, and I think, certainly, we all know monotherapy IO is relatively well tolerated. But as was discussed and described in future trial designs that have been proposed to us, we're getting IO add-ons, so this discussion is going to play into our next discussion, including voting question.

DR. HORN: Leora Horn, AstraZeneca. Your second part of your question around financial toxicities, the regimen is already out there with KEYNOTE-671, so AEGEAN would just be another treatment option for patients if perioperative therapy is what would be recommended for that patient population.

The meta-analysis that was published, it's a nice analysis. I do think that we need to see that

it was a heterogeneous patient population. It's with studies that started a long time ago, and with immunotherapy, when those drugs were first coming out, we didn't understand how to manage them as well as we do today, 15 years later with those drugs in the clinic. It also only compared neoadjuvant or adjuvant. It did not compare perioperative therapies, and in the AEGEAN study, many of the toxicities that we're seeing, the majority are actually in the neoadjuvant phase of therapy.

I'd like to call on Dr. Mayur Patel, who will go over the toxicities that we are seeing in the adjuvant phase of the AEGEAN study.

DR. PATEL: Mayur Patel, AstraZeneca. If I could have slide 1 up, please? So similar to the slide that I showed in my presentation that was looking at the overall period, this category table is looking at the events in the adjuvant period, and what you can see here is very similar to what I showed in the overall, where the unresolved, again using that unresolved, that was what we provided in

the briefing document, but when looking further, the not resolved, there were 15 events. The majority of those unresolved, even 15 events were endocrine events.

Our 12 months of therapy, I think you had talked about that, was tied to what we had known at the time, which was the PACIFIC regimen. And if I could have slide 3 up, please, this compares the safety profile of what we observed in AEGEAN with what we knew at the time of designing the study, which was 12 months of immune therapy. And what you can see here in the middle column, which is the AEGEAN adjuvant period, on the right is the PACIFIC 12-month regimen, which is approved by FDA in stage III, which was the majority of the patients in stage III. In AEGEAN, you can see the safety profile, and what you see both in terms of all-grade fatal events, as well as in grade 3/grade 4, are very similar to that. So what we see is a very consistent safety profile and no new safety findings in AEGEAN. Thank you.

DR. SPRATT: If I could actually just

follow up a question, you had a footnote that said "resolved or resolved with sequelae." Can you explain what resolved with sequelae means?

DR. PATEL: It's one of the categories in terms of how we capture the resolution of events. There are typically five categories. Resolved recalls with sequelae, where there may be some residual effects; as well as resolving, which are improving; the not resolved which haven't; and then fatal events, so there may be some symptoms. An example would be if a patient who has a stroke would have some residual weakness from the stroke, that would be captured as an adverse event with sequelae. Thank you.

DR. SPRATT: Thank you.

Alright. Dr. Conaway?

DR. CONAWAY: Yes. It looked like some of the endpoints measured at the time of surgery, like pCR, those were done after only the neoadjuvant phase, and there were some differences emerging between the treatment groups. Does that tell us anything about the relative contribution of the

neoadjuvant phase to the overall phase, since you're seeing effects from just the neoadjuvant treatment?

DR. SPRATT: Who is that question to?

DR. CONAWAY: FDA or sponsor.

DR. SPRATT: Who would you like to speak first?

DR. CONAWAY: The sponsor first.

DR. SPRATT: Yes.

DR. HORN: So, is your question specifically if the pCR rates give us information about the neoadjuvant and adjuvant phases?

DR. CONAWAY: Yes.

DR. HORN: The pCR rates that we're seeing, and to highlight, in lung cancer, I think we're excited about 20 percent pCR, but we're nowhere near where we'd like to be with the 65-plus that we're seeing in breast. So it's a small group of patients, but it only speaks to their outcome from the neoadjuvant therapy. The other parts that the neoadjuvant therapy can give us in this regimen is that we're seeing the higher rates of R0 resection

with the chemo and immunotherapy, which will allow patients, then, because patients in the AEGEAN had to have an R0 resection and have an updated scan before they went on to the adjuvant portion of therapy.

Does the FDA want to respond?

DR. GOULART: Bernardo Goulart, FDA. Regarding complete pathologic response in the trials, we will assert two things. First, at this very moment, we do not consider pCR as a clinical endpoint for regulatory approvals or a validated, quote/unquote, surrogate endpoint for EFS or OS, although there's work going on in this sphere. The second point is the analysis we're seeing here, they are exploratory and descriptive because, of course, the randomization takes place before pCR; therefore we cannot infer benefits, or lack thereof, of the adjuvant component or observation in patients who have and do not have pCR.

So those are descriptive analysis, hypothesis generating, but remember, randomization in these trials to take place before neoadjuvant

therapy, and therefore the comparison between these groups -- adjuvant and neoadjuvant, pCR, non-pCR -- do not benefit from randomization, therefore it should be considered exploratory and descriptive.

DR. LARKINS: Hi. And -- sorry.

DR. GOULART: Just let me finish my part.

DR. LARKINS: Okay.

DR. GOULART: Third, there's basically some agreement that pCR implies some better prognosis. I think this is as far as we can go with the data, but not to ascribe any potential benefits of a perioperative regimen based on pCR.

DR. LARKINS: Yes. Hi. It's Erin Larkins. I do want to note that we do agree that it does show effect in the neoadjuvant phase, and this is also why when we're talking about future 3-arm trial designs, why we lean towards including a neoadjuvant-only arm, potentially. It's a little easier to maybe consider contribution of phase for neoadjuvant, both biologically, and because you can look at path CR and ctDNA, and things like that, as

opposed to the adjuvant where it's very difficult, as Dr. Goulart was saying, to separate out the effect of the neoadjuvant portion versus the adjuvant when you're looking at the long-term outcome.

DR. CONAWAY: Perfect. Thank you.

DR. SPRATT: Alright. Thank you.

Let's keep moving a couple of minutes up at Dr. Advani.

DR. ADVANI: Ranjana Advani from Stanford. I have a question for anybody from the FDA. With the approval of 671, it sort of set the standard of care, and it's coming as an NCCN Category 1 compared to the others, where you give it only as adjuvant or only as neoadjuvant. You made the point that there's an overall survival advantage, which was not at the time of the initial thing with follow-up; it has proven that.

If this current trial under discussion with longer follow-up, but it's trending for the overall survival, if this shows that, would that be acceptable?

DR. LARKINS: Hi. Erin Larkins, FDA. As mentioned, the overall survival does not remove the issue of contribution of phase. Could it be taken into consideration as part of the overall risk-benefit assessment? Potentially. Again, I'll turn to Dr. Pazdur after this, briefly, to talk a little bit about one approval versus another, not meaning that we should continue going the same direction when we have new data emerging.

As far as the backbone issue, from baseline, the workshop that we had, it is not clear that perioperative is the standard of care throughout practice. There are many reasons why tumor boards go different ways. There are a lot of surgeons who believe that going to surgery immediately is the right course of action for patients and that treatment in the adjuvant phase is appropriate. There are others who feel like giving neoadjuvant alone upfront is enough because we haven't clearly shown that you need the adjuvant after getting neoadjuvant therapy.

So as Dr. Goulart mentioned, we do not

determine practice of medicine. If there's a clear benefit, we will -- for example, metastatic disease, once IO became established, yes, that became the new comparator arm. We're not in that situation here because we're stuck with cross-trial comparison, so it's very difficult for us to say this is the definitive new standard of care that must be used across all trials adding on new therapies.

DR. PAZDUR: Again, I want to emphasize this issue about standard of care. We do not set standard of care, period. The issue here is what the FDA does is approve a marketing application; end of discussion. That's all we're doing.

Now, the issue here is if an individual physician for an individual patient wants to prescribe a therapy, that's what's called the practice of medicine, and people do that all the time, use this drug that might be unapproved for this situation because he believes that that's in the best interest of the patient, but that does not mean that this is an approved indication.

I also want to emphasize this issue about the prior approval and just be blunt. We are not a victim of our past action, so to speak, and I want to make that quite clear to everybody. That was then and this is now, and we have new information that has come out, and we have to evaluate the situation at the current time. As was stated, even if a survival advantage was shown, that does not mean that you need this extra therapy, an extra year of therapy here.

Here again, the other issue also is moving forward with add-on designs, which are quite problematic here, and we're going to need the committee's support on this issue if you guys feel that it is necessary, because if people are not going to listen to our decisions, the only thing that we could do is put these studies on hold sometimes, and that's a very draconian action here, but that may be necessary, or prevent them from going on.

DR. SPRATT: Thank you.

DR. ADVANI: Thank you.

DR. SPRATT: Do you want the sponsor --

DR. HORN: Yes. We just wanted to make one comment. In the NCCN guidelines, the regimen is with cisplatinum doublet therapy, which is what KEYNOTE-671 had. AEGEAN had carboplatinum and cisplatin. I'd just like Dr. Gary Doherty to show the analysis that was done on AEGEAN for the cisplatinum-containing doublet. It will be super fast.

DR. SPRATT: I think we saw it showed the same as the pembrolizumab data. It was the same hazard ratio of about 0.58 in both.

DR. HORN: Correct, and we also have an overall survival hazard ratio of point 0.64.

DR. SPRATT: Yes. I think we saw it already.

We can move on to Dr. Pantelas, or I can call you a doctor.

MR. PANTELAS: Jim. No, I'm Jim Pantelas. I'm not a doctor at all. The intensification of drugs seems to be an ongoing issue. We start off trials saying maximum tolerated dosage, and we

never move off of that once we've defined it, it seems. And what we're doing here is addressing that at the front end, it seems, but I think we've got a couple of things that raise questions for me on the FDA side or the agency side.

You showed options for moving forward with a 4-arm design and a 3-arm design, and I wonder in looking at the proposed 3-arm design, one of the arms is standard of care. And I know we've talked about standard of care, but isn't it possible, through meta-analysis, to define what standard-of-care results might be to make this step a little bit more palatable?

My initial inclination is to look at things and say, "Okay. Pembro got approved, and I understand that maybe we're looking at that as a mistake or it was a different time," but out of fairness, do we look at pembro and nivolumab differently than we look at this product?

DR. SPRATT: Jim, can you just phrase the question clearly to FDA.

MR. PANTELAS: Sorry. Would the 3-arm

design accommodate use of meta-analysis for standard of care?

DR. LARKINS: Hi. Erin Larkins. You mean for future studies --

MR. PANTELAS: Yes --

DR. LARKINS: -- where we're looking to add on?

MR. PANTELAS: -- moving forward.

DR. LARKINS: Yes. So again, the discussion of what the appropriate control arm would be for this study is one we would have with sponsors as we go along. In theory, any approved therapy could be a control arm. If someone wanted to use --

DR. SPRATT: I'm sorry to interrupt you. I was told we're not going to discuss how we design these trials --

DR. LARKINS: Yes.

DR. SPRATT: -- that that's probably a very long discussion.

DR. LARKINS: Yes.

DR. SPRATT: If that's ok, we'll move on.

DR. LARKINS: Fair enough.

DR. SPRATT: Is that ok, Jim?

MR. PANTELAS: I thought these were proposed designs.

DR. SPRATT: They are. I just feel like we're going to resolve the optimal during this ODAC.

DR. LARKINS: The backbone was something we didn't want to get into because that's more something to discuss with sponsors.

DR. SPRATT: It's conceptual.

MR. PANTELAS: Exactly. But I don't know if your question was could we not have a control arm at all, and that's definitely beyond the scope of this.

DR. PAZDUR: Are you trying to emphasize an external control here; is that the issue? Because we would like to randomize studies in an adjuvant setting -- that's for sure -- not using an external control. I think that would be fraught with danger.

MR. PANTELAS: Okay.

DR. SPRATT: We can talk more, Jim.

Dr. Frenkl?

DR. FRENKL: Thank you. Tara Frenkl, industry representative. I actually have two questions, if that's ok. My first one is, I also really appreciate the proposed trial designs from the FDA. I think it gets us closer to answering this question of contribution of phases, but when I look at the proposals on read of the debrief, I had a couple of concerns that deviate from our standards. One is, first of all, the 80 percent power. Typically, industry, we do 90 percent power like the AEGEAN study on the primary endpoint; less chance of a false negative if the drug really works, and that's the sponsor's risk.

The second is really the aggressive -- the HRs -- hazard ratios that are assumed are very optimistic, and if we address both of those concerns, then we know the sample size will very, very quickly go up, and then there's real feasibility concerns. Then there are a lot of other things like dropout and other things that we consider in that feasibility. So I'm wondering how

realistic these numbers really are and how you guys considered that, and I'm sure AZ probably thought about this a lot as well, and if I could hear their perspective.

DR. LARKINS: Erin Larkins.

DR. SPRATT: Could we start --

DR. LARKINS: Oh, go ahead.

DR. SPRATT: -- with the applicant on this, actually? Just because they had shown their power calcs.

DR. HORN: Leora Horn from AstraZeneca. I'd like to call on Helen Mann from Biostatistics to answer this question, please.

MS. MANN: Helen Mann, Statistics. There were elements there that you talked about in terms of powering, and I guess what we presented was looking at powering for the contribution of phase for 80 percent power, but we acknowledged that was really to give an indication. We didn't have any guidance for how to power the contribution of phase at the time, so that's why we gave that. But we have looked at it, and we could certainly present

options where we have smaller and larger studies that look at a different power for the contribution of phase. It's a problem as an industry, and we're looking into how that is addressed.

I think there's, obviously, another issue around dropout rate; again, what we've looked at as an important consideration. We have in some of our sample size trials looked at that, and we need to build that into future designs that we all look at. When we've looked at and thought about the timing and the number of patients, that's made the durations of the trials longer.

DR. FRENKL: Sorry, just one question. So the 80 percent power is for looking at the difference between, for example, the 3 arm, the neoadjuvant and the perioperative regimen.

MS. MANN: Yes. I presented before the examples of AEGEAN, and that's why the studies were --

DR. FRENKL: About 2500 patients or such?

MS. MANN: -- yes.

DR. FRENKL: Okay. Thank you.

DR. FORD: I'd like to invite Dr. Mishra-Kalyani to answer from FDA's perspective.

DR. MISHRA-KALYANI: Thank you very much for the excellent question. I'm Pallavi Mishra-Kalyani from FDA Statistics. Just to clarify, in the sample sizes provided in the briefing document, as well as those presented today from FDA's side, the primary comparison does have 90 percent power. We did consider lower power for some of the other comparisons, but the primary comparison of perioperative setting compared to standard of care does have 90 percent power.

I should also say that all of the assumptions that we used for our power calculations were informed by observed results from all the perioperative trials that have already read out. We looked at dropout rates, we looked at control arm medians, we looked at survival rates, and we included all that information. So we feel like we took a very reasonable approach to understanding what a sample size might look like in these

settings.

It's important to note, again, that every sample size is based on the treatment effect size. The larger and more clinically meaningful treatment effect, which is what we are hoping for, for our patients moving forward, will result in smaller sample sizes. If there's a marginal effect, your trial is going to need to be much larger in order to demonstrate that treatment effect. Thank you.

DR. SPRATT: Does that answer your question?

DR. PAZDUR: As a teaser for the discussion coming up --

DR. SPRATT: Can you state your name, please?

(Laughter.)

DR. PAZDUR: Richard Pazdur, FDA.

DR. SPRATT: Thanks.

DR. PAZDUR: As a teaser for the discussion coming up, one of the things that we should consider also is pragmatic trials in this situation. This is an ideal situation for a large, pragmatic, simple trial with survival as an

endpoint. Because these drugs usually have very well-known safety profiles before they get into the adjuvant setting, they could have very minimal, if any, safety, actually, assessment because the safety of these drugs are quite well known and very broad eligibility criteria. These would be large trials, obviously. They probably would be overpowered in a sense because we're looking at demonstration of -- because there's a lot of noise in these trials. But this is a consideration that we should have in this setting.

I'd just like to emphasize this is something that the FDA is very interested in. We have a project called 5 in 5, looking at suggestions for pragmatic trials. But this tends to be an ideal situation where some of these answers can be obtained, especially since we know the safety of many of these drugs by the time they get to this situation.

Just to give a brief discussion of a point of the current pragmatic trial at the NCI that's being done in advanced lung cancer, this trial

really went off gangbusters. It had very rapid accrual, and what's even more important, it has accrual of minority groups that have been unprecedented into the NCI accrual structure here. So when you have a simple trial with a simple informed consent, people want to go on it. They understand what's going on, and we only have one basic question here, ultimately, is, does this improve overall survival?

DR. SPRATT: Thank you.

I have one final clarifying question -- my name is Dan Spratt -- to the FDA. I know we're running short on time. We keep talking about contribution of phase, but this assumes that the therapeutic sequencing around an event -- in this case, surgery -- has a proven interaction. So we can talk about duration, sequencing, and Dr. Heymach nicely noted with chemotherapy, ignoring the toxicity or getting to surgery, there is no clear difference in neoadjuvant/adjuvant approaches. Often, there are other advantages of neoadjuvant therapy. It has not been clearly borne

out that there is an actual proven -- there's preclinical -- interaction of sequencing with an event. If we all did preclinical, we would all give radiation in IO and pretend we'd get abscopal effects everywhere, which in the lab works great; in clinic, not so much.

So can you please direct -- is this really a sequencing specific or phase of contribution, or how do you separate that from duration of therapy if these trials were 2 cycles neoadjuvant and 1 cycle adjuvant? Are we just making this up as this magical event of neoadjuvant and adjuvant? Because I would think duration, when you talk about financial toxicity as well as physical toxicity, is what is bankrupting patients, is prolonged durations with no clear need for those durations.

DR. KLUETZ: Yes. This is Paul Kluetz with the FDA. I think it's a great question, Dr. Spratt. I think, obviously, the longer duration you have, the more safety risk you have, and the more concern we have; and, in fact, that again plays into the second question. It's going

to be more safety risk when you have IO plus new drug in both sequences.

I think the key is teasing out neoadjuvant, the actual specific phase. Right now, that's all we can do. Generally speaking, they've been given a similar duration from the adjuvant perspective, but certainly the longer it goes, the more risk to the patient, and the more we would be concerned that there's uncertainty around the need for the adjuvant phase.

DR. SPRATT: I would just say it's probably something that should be defined because before you know it, you'll have a year of neoadjuvant therapy in certain diseases, and then you'll ask the question, do you need a year?

Thank you. We are right at 11:45, so we will now break for lunch. We will reconvene again in this room at 12:15 pm Eastern Time. Please take any personal belongings you may want with you at this time. Panel members, please remember that there should be no chatting or discussion during the lunch break. Additionally, you should plan to

reconvene at around 12:10, for the panel members, to ensure you are seated before we reconvene at 12:15 pm. Thank you.

(Whereupon, at 11:45 a.m., a lunch recess was taken, and meeting resumed at 12:16 p.m.)

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

(12:16 p.m.)

Open Public Hearing

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

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

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

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

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

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

You will have five minutes.

DR. STILES: Sure, and thanks for the privilege of the floor. My name is Brendon Stiles. I'm the Chief of Thoracic Surgery and Surgical Oncology at the Montefiore Einstein Comprehensive Cancer Center in the Bronx, and I've served on advisory boards and in consulting positions for AstraZeneca and for other pharma companies.

I've been involved with several neoadjuvant and adjuvant trials, and I'm also active in the lung cancer advocacy community, having previously served as the Chair of the Lung Cancer Research Foundation, where I currently serve as the Vice Chair of the Board and as the Vice Chair of the Scientific Advisory Board. I also serve on the Scientific Advisory Board of Lungevity.

Additionally, I'm on the Board of the European Society of Thoracic Surgery and the ATS Foundation Advisory Council, and I was the senior author of an expert consensus document review and making recommendations for surgeons on neoadjuvant and adjuvant periop data.

I strongly believe that we need to have multiple treatment options for our patients. The EFS primary endpoint with a hazard ratio 0.68, favoring the addition of neoadjuvant and adjuvant durvalumab to neoadjuvant chemotherapy alone, clearly meets the definition of efficacy that we clinicians look for as comparable to what we've seen with other regimens.

As mentioned previously in the discussion, the key distinguishing factor of the AEGEAN regimen is that it included patients who were treated with neoadjuvant carboplatin and cisplatin rather than just cisplatin as done in the KEYNOTE-671 trial, and I think the trials really are not comparable given that distinction. AEGEAN therefore extends the benefit of combination therapy to those patients who may be unable to tolerate cisplatin. While the FDA acknowledges that providers may use pembrolizumab with carboplatin in the neoadjuvant setting, I think we have to acknowledge that they do so with a distinct lack of level 1 evidence.

Now, critical for me as a surgeon is also

the explicit understanding that as many as 20 percent of my patients referred for neoadjuvant therapy may not make it to surgery. This is an important group of patients for the AEGEAN treatment paradigm. I think we must acknowledge the definitions of resectability are changing. It's likely that even more marginal resectable patients will begin on neoadjuvant therapy in the future.

For me and for patients in this scenario, it makes total sense to start with durvalumab here so that the same immunotherapy could be used in the adjuvant setting for those patients who do not get surgery and instead get chemoradiation. The PACIFIC trial firmly established the benefit of durvalumab in this setting where it's the standard of care, and I will preferentially use this regimen in marginal resectable patients so that they don't have to change immunotherapy agents should they instead get treated with chemotherapy and radiation, which I think is perfectly appropriate.

I'm supportive that the FDA should require

the new trial design proposals for phase 3 studies of perioperative regimens for resectable non-small cell lung cancer include adequate within-trial assessment of contribution of the treatment phase, and while I appreciate the value of the smart design proposed for future studies, I don't believe the lack of it in this trial should unfairly exclude patients from receiving this combination.

I do believe that we'll see a benefit to adjuvant therapy in non-complete path responders in these trials. I don't expect the overall magnitude to be huge, but I do expect it to be clinically meaningful for certain subgroups of patients. I think we need more uptake and use to discover which patients those are.

Finally, despite the remarkable improvements we've seen in the treatment outcomes of patients with lung cancer with neoadjuvant therapy, I had the sobering experience of having a patient return just a couple weeks ago to me with progression after having a significant pathological response to neoadjuvant therapy-only regimen.

Over a third of patients are suffering recurrences or dying by just two years at follow-up in these trials, and I think we all need to remember that we need to responsibly set the stage and partner with industry to bring novel drugs to the clinic to improve the neoadjuvant response and decrease recurrence with adjuvant therapy.

AstraZeneca's COAST and NeoCOAST platforms adding anti-CD73 and anti-NKG2A antibodies to durvalumab are great examples, I think, of where signals of efficacy have already been demonstrated, and the ability to further advance these therapies in the neoadjuvant space to improve outcomes for patients I think will be highly dependent upon approval of the AEGEAN regimen.

So for these reasons, use in patients unable to tolerate cisplatin; delivery of single immunotherapy drug for patients who don't make it to surgery and instead are treated with chemoradiation; and the opportunity for improvements in outcomes, on behalf of my patients, I strongly encourage the FDA to approve the

treatment regimen. Thanks for the privilege of speaking today.

DR. SPRATT: Thank you so much.

Speaker number 2, please unmute and turn on your webcam. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you are representing for the record. You will have five minutes.

MS. DREW: Thank you, and thank you for the opportunity to speak today. My name is Grace Drew. I'm a medical student at the University of Texas Health Science Center at Houston, and today I'm speaking on behalf of the National Center for Health Research. Our nonprofit research center analyzes scientific and medical data and provides objective health information to patients, providers, and policymakers. We do not accept funding from pharmaceutical companies or any company with financial ties to our work, and therefore we have no conflicts of interest.

We appreciate the chance to participate in FDA advisory committee meetings like this one,

which bring together experts to examine data based on complex treatment regimens. We agree with the questions raised by FDA scientists about whether the trials conducted under durvalumab adequately address the possible benefits of perioperative treatment compared to neoadjuvant or adjuvant treatment.

We all understand the need for improved treatments for non-small cell lung cancer. Patients deserve the best possible treatments based on the best possible evidence. Obviously, overtreatment can be as problematic as undertreatment because excessive drug dosing can cause unpleasant or dangerous adverse effects, toxicity, as well as a significant financial burden to patients.

We agree that the AEGEAN trial met its primary endpoint by demonstrating a statistically significant and clinically meaningful improvement in event-free survival; however, we agree with FDA scientists that the design of the AEGEAN study does not allow for a within-trial assessment of the

individual contributions of durvalumab given concurrently with chemotherapy in the neoadjuvant phase compared to durvalumab given in the adjuvant phase. This is especially important because emerging data from completed trials of neoadjuvant-only, adjuvant-only, and perioperative immune checkpoint inhibitor regimens across other drugs in the class raise questions about the need for immune checkpoint inhibitors in both perioperative phases of therapy.

Even more important, we agree with the FDA's concern that the AEGEAN trial indicated a non-significant reduction in disease-free survival in the patients that received durvalumab both before and after surgery. Since it is not statistically significant, this could have occurred by chance or could be a lasting effect of durvalumab in platinum chemotherapy treatment before surgery. This non-significant finding contributes to the uncertainty about whether it is beneficial for patients to receive durvalumab both before and after surgery rather than one or the

other.

We agree with the FDA scientists that it is not appropriate to conclude that durvalumab improves disease-free or overall survival, although we also agree that the data suggests that durvalumab probably doesn't reduce disease-free or overall survival. While the overall survival rate exceeded expectation, it was not significantly greater than the overall survival of the placebo patients, and therefore could have occurred by chance. In addition, the results may be biased because the patients in the modified resected set may have differed from the placebo group in ways that affected disease-free survival. Thus, we cannot conclude that durvalumab given both before and after surgery improved overall survival.

In conclusion, the one statistically significant benefit, event-free survival, could have been due to durvalumab given either concurrently with chemotherapy in the neoadjuvant phase or in the adjuvant phase. The other results show no statistically significant benefit in terms

of disease-free or overall survival. The FDA is responsible for making a decision based on studies that are adequately designed to address the benefit of perioperative treatment as compared to neoadjuvant or adjuvant treatments. Unfortunately, better designed trials are necessary to determine the safest and most effective regimen for durvalumab therapy. Thank you.

DR. SPRATT: Thank you.

Speaker number 3, please unmute and turn on your webcam.

DR. ONDA: Thank you. Mr. Chair, members of the committee --

DR. SPRATT: Real quick, sorry, one second. Will speaker number 3 begin and introduce yourself? Please state your name and any organization you are representing for the record. You will have five minutes. Thank you.

DR. ONDA: Mr. Chair, members of the committee, thank you for allowing me to speak today. AstraZeneca has not provided any financial support for my testimony today. My name is Pierre

Onda, and I'm a recently retired primary care physician. Today, I'm here not as a recipient of durvalumab but simply as the spouse of someone who took it for over a year. I hope to share how my perceptions of terms like "likelihood of improved progression free survival" or "chances of improved survival rates" have changed through my personal experience.

My wife Heidi was diagnosed with late-stage, unresectable, non-small cell lung cancer in October of 2018. She will be testifying shortly. On October 15th of 2018, while I was in my office seeing patients, Heidi's gynecologist called me. He wanted to let me know the results of her CAT scan that he had ordered as part of an evaluation of an atypical cyst she had. He was unable to reach her, but I had HIPAA release, and his office was just down the hall from mine, and he wanted to discuss the results with me in person. He informed me that while Heidi's ovarian cyst had shrunk and appeared benign, the radiologist had noted something abnormal in her lung.

I rushed to his office, and I had already pulled up her chest CT. I was hoping to see something like a small granulomatous nodule, but I saw a very frightening looking mass in her left upper lobe. I then scanned the report and was devastated to read the following, quote, "2 and a half centimeter spiculated nodule; would favor bronchogenic carcinoma with malignant mediastinal lymphadenopathy; recommend PET CT or CT-guided biopsy."

Please try to put yourself in my shoes. The subsequent PET scan, biopsy, and reviews by two tumor boards confirmed inoperable stage IIIA, non-small cell lung cancer, and the treatment plan recommended was for concurrent chemoradiation followed by one year durvalumab infusions. At the time, I knew very little about durvalumab. All I could focus on was really the evaporation of the future plans I had for us.

My research through Google and Ovid presented Kaplan-Meier curves with pretty dismal survival rates for her stage. Fortunately, Heidi's

medical oncologist informed us that durvalumab had been approved and included in the NCCN treatment guidelines just a month before her diagnosis. He shared data from the PACIFIC trial, highlighting that, quote, "The median time to death or distant metastases was 28 months in the durvalumab group compared to 16 months in the placebo group, along with numerous side effects," but before Heidi's diagnosis, I underestimated the significance of treatment outcomes like these, and now I see any extension of time, or the possibility of time, a day, a month, or a year, is invaluable.

Reflecting on the past 66 months since Heidi's diagnosis and everything we've experienced together, I value every moment. Almost irrespective of duration, each day offers the chance for unique and wondrous experiences: another hike through a beautiful forest, witnessing our child's wedding, the birth of a grandchild, or simply enjoying a quiet evening watching a movie together.

So as you deliberate on the risks and

benefits and evidence-based data of the proposed therapeutic indications, please consider the value of time from the perspective of those affected by the treatment options you are considering. Thank you for your time and for the challenging work that you do.

DR. SPRATT: Thank you so much.

Will speaker number 4 please unmute and turn on your webcam? Will speaker number 4 begin and introduce yourself? Please state your name in any organization you are representing for the record. You will have five minutes. Thank you.

MS. NAFMAN-ONDA: Yes. My name is Heidi Nafman-Onda. I am a lung cancer survivor advocate. I'm representing myself, and I have no connection to AstraZeneca for this testimony today.

So this is us. This is me and my family. Being a lifelong health enthusiast, health educator, and a fitness trainer, my family and I were shocked with my stage IIIA inoperable lung cancer diagnosis in October of 2018. What was really scary about this was that I had no symptoms.

This was an incidental finding while investigating another health issue. I had no biomarkers come back and no PD-L1, so I was inoperable, and I was told that I was pretty much terminal within 4 to 6 months and to get my affairs in order. But then I was given so much hope by my oncologist. He told me about durvalumab, which had been recently FDA approved prior to my diagnosis, and that if I didn't progress after chemoradiation with cisplatin and pemetrexed, and 30 radiation treatments, that I could get this new immunotherapy every other week for a year.

I experienced with durvalumab some side effects, but I always refer to them as nuisances because they really didn't affect my quality of life. I would get some mild aches and pains muscularly and sometimes joints in my hands, which were mitigated by taking ibuprofen, and I always had a mild case of psoriasis throughout my life, and it elevated to a moderate case, which I still have today, and a little bit of dry mouth.

These are my scans. Here's the incidental

finding in October of 2018 and my most recent scan in April of 2024. I am very, very grateful for the FDA approval of durvalumab in 2018, and I live a quality of life that is very important to me, and I have now been able to witness the marriage of another child after my diagnosis and 2 grandchildren that were born within 4 months of each other in 2023.

I appreciate you giving me the opportunity to be seen today because I am one of those dots on the graphs that you look at in terms of data. I appreciate you seeing me today. We are a family, and we appreciate research and the hope that it gives to others, and I hope that this can also help surgical candidates, people who are diagnosed earlier than I was. Thank you.

DR. SPRATT: Thank you so much, and appreciated.

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

You have five minutes.

MS. JONES: Hello. My name is Janise Jones. I'm a lung cancer survivor. I have no connections to AstraZeneca. I'm a 54-year-old wife, mother, and grandmother. I was diagnosed with stage IA, non-small cell lung cancer October 2018. From there, November of 2018, I had a lobectomy done to remove the right upper lobe. After that, 3 months later, I went in for a follow-up CT scan after surgery, and they noticed a lymph node on my chest was inflamed. It was recommended for them to keep an eye on it and for me to have another CT scan 3 months later. I did that in May. It came back, and it was 2 times the size it was prior.

From there, I had to do a PET scan for staging, then an ultrasound of the lymph node, and after that, I started chemo, aggressive cycles of 3 chemo cycles, then aggressive chest radiation 5 days a week for 31 days. After I was done with treatment in August of 2019, October of 2019, I started my immunotherapy treatment, and it lasted till November of 2020.

As far as side effects, they weren't bad. I was feeling nauseated, weakness, a lot of fatigue, body aches, but it was nothing that stopped me from doing my day-to-day tasks. I firmly believe that with me doing immunotherapy, it has kept me in NED ever since, and I'm grateful for that. I feel that it was the best choice that my oncologist made for me, and I feel their research is very important and it does matter. Thank you.

DR. SPRATT: Thank you so much.

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

MR. BJORK: Thank you very much for this opportunity. My name is David Bjork, and I'm speaking on behalf of myself, and I do not have a financial relationship with AstraZeneca for my testimony today. I'm a lung cancer survivor, patient advocate, and research evangelist. I'm a member of the IASLC Patient Advocacy Committee and

the Stars Scholar Program. I'm also a member of the Patient Insights Board of Medidata.

The Greek meaning of evangelist is bringing the good news. I'm always hoping for more good news about treatments for lung cancer. I'm speaking here today on behalf of the lung cancer community and those people affected by a lung cancer diagnosis: patients, care partners, families, and healthcare providers. As we all know, in 2024, 325,000 people will die from lung cancer in the United States, and it's by far the leading cause of cancer death.

I'm here to share that it was devastating for me when I got my diagnosis, and I was diagnosed several years ago when I was a healthy 35 year old with three young children under the age of 6. There were no good treatment options then, and I will never forget how I felt when my doctor called me and said, "Dave, you have lung cancer. You need to come see me." All you need to do once you're diagnosed is to look up the statistics and realize that your chances of survival are not good. I was

devastated, but I'm grateful that I had a good outcome after my lobectomy, and I hope now that other people can have the same outcome as I did.

Over the past several years as new treatment regimens have been approved, this has given so much hope to patients and families, and every new treatment means so much to our community and to the healthcare providers that can bring positive news to patients that will benefit from these new treatments. We all get so excited about how targeted therapies and immunotherapies have transformed outcomes for non-small cell lung cancer patients, and we know that early stage is where we can intervene to maximize our treatments.

The AEGEAN study adds treatment choices for patients with resectable non-small cell lung cancer, but more needs to be done. I'm not a scientist, but my understanding is the AEGEAN trials have been studied by as much benefit for patients as possible, and that's what matters to me, and that's so important to people like me and friends who are affected by lung cancer. Every new

treatment option brings real hope and gives people time, and time is so valued for a lung cancer patient. I have friends who think of time in terms of months being a lifetime because that might be all the time they have left; it is that urgent.

Lung cancer is such a deadly disease, and getting a diagnosis is so different than these other diseases. I firmly believe that we need to act with a sense of urgency. I have personally lost many friends to lung cancer in the past few years, which has had a profound impact on me. The disease burden for lung cancer is very high, and experiencing things like worrying about the next scan or not knowing the outcome is heart wrenching, and it's beyond what most people can even comprehend.

I'm a person that believes in empathy and more empathy in our healthcare system, so if a member of your family was diagnosed with lung cancer, how can you feel? Any new treatment that brings better outcomes is what gives hope and real benefit to patients and families. In closing, I

want to say that in spite of the good news, I believe that there's still unmet need to bring more treatment options to people affected by a lung cancer diagnosis, and I'm super grateful for this opportunity to share my perspective with you today.

DR. SPRATT: Thank you so much. I'd like to thank all the speakers.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. I'm going to move forward, in that I feel everyone had asked clarifying questions, so I'm going to move forward to the discussion unless someone feels it is a very important clarifying question.

(No audible response.)

DR. SPRATT: So then I need to read the following.

(Laughter.)

Clarifying Questions (continued)

DR. SPRATT: As we have additional time, we will now take remaining clarifying questions. Please remember to state your name for the record

before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. As a gentle reminder, it would be helpful to acknowledge the end of your question with a thank you and end your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Are there clarifying questions for the presenters?

DR. FRENKL: Tara Frankel, industry rep. I just had a question because FDA brought it up about BR.31, and I noted that it was a slightly different population. So I wanted to ask the applicant if they could elaborate on if there's any considerations that we would have when considering that different patient population, knowing that the data is embargoed until whenever it's going to be presented. I'm not sure when that is.

DR. HORN: Leora Horn, AstraZeneca. I'd like to call on Dr. John Heymach to maybe describe

the difference between a group of patients as they're being selected for therapy or perioperative study versus an adjuvant study.

Dr. Heymach?

DR. HEYMACH: Thank you. John Heymach from MD Anderson. For those that don't treat lung cancer, I just thought I would describe in detail what the difference between an adjuvant study is and a perioperative study, and how these populations really are very different.

If I could get slide number 4 up? Recall in a perioperative study, or a neoadjuvant study, the randomization occurs before the beginning of any treatment. So you've got neoadjuvant therapy, and in every study that I'm aware of, and there've been many studies done with neoadjuvant therapy, the dropout from the time of that initial randomization to surgery tends to be 15 to 18 percent, and there's remarkable consistency there.

Now, after surgery, then you move on to adjuvant immunotherapy, and typically about 65 to 68 percent of patients make it to the adjuvant

phase. I just want people to remember, one-third of the patients drop out before they make it to adjuvant, so the group that makes it to adjuvant therapy is only the two-thirds of patients that have the best prognosis; that successfully had an R0 resection. And remember, a lot of patients go into surgery and are found to not be operable, you do an exploratory thoracotomy, and then you stop it. At that point, all those patients are taken off the board when it comes to an adjuvant study, so they never make it to the study.

When you get to an adjuvant study now, it's only the best two-thirds that made it through, had the R0 resection, had chemo, and want to proceed. If you look at DFS then, that's the two-thirds of patients who already made it through. So when you're comparing an adjuvant study to a perioperative study, any hazard ratios you see dramatically underestimate the true difference in benefit if those patients were to get randomized from the beginning because, again, one-third of the patients that drop out all around the ledger, if

you will, for the perioperative study, they never get on the ledger for patients in the adjuvant setting.

So if you go to the number 1 slide please, that setting, you'll see the numbers here for the adjuvant studies, the 0.81 and the 0.85 for the KEYNOTE-091 and the IMPower-010. Those numbers that were put up are different than the ones you saw before from the FDA. The difference here is we're showing all the PD-L1 levels because the perioperative studies included all the PD-L1 levels. We're not showing just the selected PD-L1 levels that the FDA label for the IMPower-010 include.

So when you include apples to apples of all PD-L1 levels, you see the hazard ratio is 0.81 to 0.85, and for the perioperative, 0.59 to 0.69. But again, that underestimates the true difference because of that one-third of patients that drop out before you ever get to the adjuvant study. So this is really just to highlight that the populations are very different between the adjuvant and the

perioperative.

The last point I'll make, we don't typically put more advanced patients who have N2 nodal disease on to pure adjuvant studies. Those patients, the ones with more advanced disease, we typically want to put on a perioperative or neoadjuvant study because neoadjuvant very commonly downstages patients, expands the number, and they're potentially resectable there. And for that reason, 49 percent of the AEGEAN patients who had N2 disease, 71 percent were stage III disease. So the perioperative population is a more advanced population than the selected patients who make it through into the adjuvant setting. Thank you.

DR. SPRATT: Is that sufficient?

(No audible response.)

DR. SPRATT: Okay.

I guess to add on to that, in the slide shown, only 470 out of 800 patients on the AEGEAN trial were resected, so that's the resected population. So it goes back to, these patients, as a radiation oncologist, should they be having

surgery?

(Laughter.)

Questions to the Committee and Discussion

DR. SPRATT: But anyways, we will move now forward.

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

We'll proceed with our first question, which is a discussion question. In light of the uncertainty around the need for both phases of treatment, discuss whether an additional trial should be conducted to clarify the contribution of treatment phase for the durvalumab perioperative

regimen prior to approval.

Are there any questions regarding the wording of this question?

(No response.)

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

Dr. Lieu?

DR. LIEU: This is Chris Lieu, University of Colorado. I'll just open up the way I perceive the data. We have two agents, pembrolizumab and durvalumab, in a perioperative setting that show positive results. We know that something about this strategy improves event-free survival, and when you look at KEYNOTE-671, there's an overall survival benefit.

So when you look at the risks -- and I think this is really obvious -- what are we worried about? It's that we're giving a year of adjuvant therapy and potentially harming patients in that without any survival benefit. And we just don't know the answer to that, and I think that that's a

legitimate risk. But again, the second thing to consider is that if you require a study to determine the benefit of each phase of treatment, you're looking at a 6-plus year time frame of trying to answer that question. And the problem with that, and to go to the extreme, if we apply that standard to pembrolizumab, then you're denying patients access to medications that we know work in terms of disease-free survival and maybe overall survival for 6 years just to figure out which phase is working.

I think that's a very, very critical question, but I also don't want to prevent access to at least what we think is a winning strategy, something about that is a winning strategy, so I'd like to put that in the hands of the patients and the physicians. I think there's obviously a lot of confusion about the state of the field and what the data shows, and I understand that the current trials are not perfectly answering the question either.

CCTG gives you a little bit of data in the

adjuvant setting, although Dr. Heymach made a great point about that patient population, and then we have some cooperative group studies that will answer this question. SWOG has a path CR study that will start to answer this question because we believe a lot of this therapy benefit is in the neoadjuvant setting, and then we have an upcoming cooperative group study that will help answer the question of the non-path CR. So I think in the time frame, I think we will get some clarity, but in the meantime, I'd like to have this as an option available to patients and their providers.

DR. SPRATT: Dr. Lieu, this is Dan Spratt. To push you on this a little further for discussion, the applicant sample size for a 3-arm trial extended the duration about 2 years and change, and to say something very provocative, AstraZeneca in 2023 generated $4.3 billion from durvalumab. About 2 days of revenue, you could generate probably enough to get one more arm of trial for 2 years of data and patients. That's a year of therapy. The financial toxicity part of

this is substantial; it's hundreds of thousands of dollars.

So do you really think -- because this was discussed prior to the onset, I agree if you're moving the puck after, whether fairness is even relevant. We now are left with the patients to take this burden, so can you respond to that?

DR. LIEU: This is Chris. I think it's a great point. I think it's a question that has to be answered, and the question that we're really tasked with here is should we delay the availability of therapy for this amount of time to answer that question? And I think that it would be reasonable for people to go both ways on this.

What I would say is that, again, because the strategy has shown disease-free survival benefit and in one trial overall survival benefit, that should be available now while we answer this very critical question. Then, I know what we're going to get on moving forward is, "Well, what should the future look like?" And I'm sure we're going to talk a lot about that, but I don't think it should

look like this.

DR. SPRATT: I want to go out of order because you asked the question, Dr. van Berkel. As a thoracic oncologist, surgical oncologist, you asked a question earlier, we've got multiple options on the table here with variably similar EFS rates. I guess to ask you the question, if you have a patient where you can give a perioperative regimen versus a neoadjuvant-only with all the flaws of cross-trial comparison with similar EFS hazard ratios of benefit, if we turned the table on you, how would you answer that question?

DR. VAN BERKEL: Sure. I'm Victor van Berkel, again, from University of Louisville. I think it's important to say that as a surgeon -- thankfully or unthankfully, I suppose, depending on how you look at it -- I don't end up having to have that conversation too often because when it comes to me, I end up operating on somebody, and then we say, "Alright. You either need to see the medical oncologist or you don't."

When it comes to having discussions about

neoadjuvant therapy, however, my world has changed a great deal in the last couple years with the trials that have come out because now we have to consider neoadjuvant therapy for people that otherwise we would have just taken to the operating room and worked on, and if we found something surprising afterwards, they would get treatment.

Of course, every time someone comes to me in a post-operative setting, and I have to tell them, "Yes, now you're going to need some treatment," they're there full of questions, and of course I try to answer them as best that I can. And I think, unfortunately, the answer that I have to tell them is that I don't really know what the right answer for them is. And, of course, their question is always like, "Well, if you were me, or if I was your mom, or if I was your sister, or whatever, what would you do?" And it's hard for me to look at some of this data and be able to give them a clear answer about that.

I should be clear about this as well. I love immunotherapy. It's incredible, and the

impact that it's had, especially in Kentucky, because everybody freaking smokes -- we have cancer out the wazoo in Kentucky, and the impact that immunotherapy has had in our community in the last 5 years, in taking people who are stage III and stage IV and giving them meaningful existence afterwards, is incredible, and it's been a wonderful thing to see.

My dad died of stage IV lung cancer before this was an opportunity for him, and I regret that every time that I think about it. So I am very much in favor of immunotherapy and the benefit that it has done for people, but that's clear for stage III and stage IV patients. Me, I tend to see people at the earlier stages, and a lot of these adjuvant therapies, the benefit is kind of marginal sometimes.

Knowing how to balance that, the potential risks of their treatment -- for example, in the studies that were put up here, there was a 1 percent overall mortality rate from the immunologic adverse events. That's not

insignificant. It's not zero. It's not high, and most of the impact is relatively minor. And I always tell people, immunotherapy is a lot easier to deal with than chemotherapy is, for sure, but it still has problems.

So this is a very rambling way to tell you I don't know how to answer that question for people. I think, unfortunately, I don't know that we're going to -- to speak to what Dr. Lieu was saying, I worry that trying to get an answer to that question is going to prevent people from getting care that they would benefit from, and finding that balance is, to be sure, a challenge.

DR. SPRATT: Thank you.

Dr. Madan?

DR. MADAN: Yes. Thank you. Ravi Madan, medical oncologist, National Cancer Institute. I think that the question here is important because we need to figure out what the contribution is of all the therapies we're using in clinic; and it's getting more and more complicated with the proliferation of options that are available, but I

think we need to be more deliberate in how we design these trials.

Now that having been said, we're on a path that was set forth six years ago and whatever happened, happened, and now we're here with data that's pretty good for patients, and you can't unring that bell. So as a purist and from an idealist perspective, it would be great to do this trial, and it would take 5 to 6 years. You did the cost analysis, and that was pretty good.

But there's a pragmatic component here of how do you tell a patient that we've got some data, it's pretty good, and it may be adding a little bit of added toxicity? Fortunately, the immunotherapy is not adding a ton of toxicity here, but it's a little bit of an individual roll of the dice for patients to say I'm going to forgo what standard options are and do a trial where I may be getting less than is helpful for me. I don't know how I would handle that. I'm kind of leaning in towards not doing a trial like that, and that's going to be a huge obstacle for accrual, so some of these

timelines that we're kicking around could be a lot longer. Then you create a situation where we've got to go to other regions of the world, and then it creates an ethical dilemma of should we be doing this at all in those environments just because they're in a different part of the world?

So I do hope that we'll get more understanding from ongoing trials and future data, and we can revisit this, but I think to delay this at this point is very complicated for patients and their providers.

DR. SPRATT: Thank you, Dr. Madan.

To that point, they showed the data from PACIFIC-1, which is practice changing. I think many of the open public hearing speakers were basically treated on the PACIFIC regimen and clearly very impactful. Not shown was PACIFIC-2, which was concurrent and we'll call it adjuvant or consolidated therapy, which was negative. So the standard still remains just the adjuvant or consolidated therapy.

A question that comes up is if you had just

run all of that in one trial and, A, if they started with concurrent and adjuvant, you would have just killed this option for patients saying this doesn't help when actually it has a massive benefit, as we heard from speakers and the data, so it goes both ways. It's nice when it's positive, but it can go the opposite way as well. I guess I still question is 2 years too long to wait for the potential for decades to come, but very valid points that you bring up, of course.

DR. MADAN: Ravi Madan, NCI. I would just say that part of what the future should entail, as Mr. Pantelas highlighted earlier, is we start off big and then de-escalate, and I would hope that there would be trials in the future, maybe say 6 months versus 12 months. Maybe that can be done. Maybe that's done in a cooperative group. So I do think there are ways to re-evaluate this over time. The question is, is the immediate delay required and feasible?

DR. SPRATT: Thanks.

Actually, Dr. Mitchell, I believe is on

Zoom. Sorry. Mr. Mitchell.

MR. MITCHELL: Yes, I am Mr. Mitchell. I'm the consumer representative for today's ODAC, and I want to start from a consumer perspective. Folks keep mentioning the issue of the cost of treatment and they have it go on for a year. I always try to bear in mind that the job of the FDA is to decide whether a drug is safe and effective and it doesn't have a direct role in cost. Whether we take that into account or not as an advisory committee I suppose is another matter.

But the question here has nothing to do with cost, and Dr. Lieu and Dr. Madan both have touched on how I think about what I have heard today and read in preparation for this meeting. This drug and this trial met its primary endpoint, and patients were helped, and it's kind of that simple for me. I also happen to be a multiple myeloma patient that takes 4 drugs right now, a lot of drugs, very expensive, and side effects.

But the question is, should we require another study that would extend the time before

people get access to this drug that has been shown to meet the primary endpoint, it has been shown to help patients, and should we require that before the FDA allows approval? My answer would be no, we shouldn't. We should make this drug available because it helps patients now.

What took place -- someone mentioned 6 years back -- is kind of like water under the bridge, or over the dam, whichever you like. We have before us something that can help patients, and the toxicities appear to be tolerable. We don't know whether it's the neoadjuvant phase or the adjuvant phase; we don't, but we know that it does help patients.

So I do not think that we should be requiring a study to determine which phase of treatment is doing what, now, prior to approval, but we're going to talk, I think, next about whether we should be requiring studies in these circumstances that address that question in the future, so I will be discussing that issue in that context when we get to the next question. I hope

that was clear.

DR. SPRATT: Thank you, very helpful.

Mr. Pantelas?

MR. PANTELAS: Jim Pantelas. As somebody that's lived through a diagnosis of lung cancer, has been through surgery, chemo, radiation and 18 years of life since then, I have to say I know most of the people that called in. This is a very tight community and we're losing too many people daily.

We have a product here that has strong indications of working. I mean, we've got proof that it is helping. I understand the concern about the 1 percent death rate that may be attributable. When I was diagnosed, I was given less than 2 percent chance of making it to 2 years, so from a patient perspective, I think every patient would take that gamble. Ninety-nine percent you'll survive and 1 percent you won't, for a lung cancer patient, those are wonderful odds.

I think what we're asking here is the right question but maybe in the wrong way. Is there a

way to incentivize the drug manufacturers of these three drugs to do the add-on work to look at a de-escalation of the drug if we approve this? I'm all for de-escalating the amount of drug that we're asked to take, but I wouldn't take this away from the community.

DR. SPRATT: Thank you so much.

Dr. Rosko?

DR. ROSKO: Ashley Rosko. The one point that I also wanted to bring up was about three-quarters of these patients received carboplatin as part of their neoadjuvant therapy, which a lot of clinicians use in practice, so it provides that additional support and additional added benefit for patients in the perioperative setting to receive a drug that they would commonly receive anyways.

Then I just also wanted to mention about the adjuvant therapy in terms of that one year. I do trust that clinicians are comfortable with the side effects and toxicities of this therapy and that if a patient were to be experiencing adverse events,

that they can discontinue the therapy as an option as well. I think this study as it's been designed doesn't answer the question about phases, and, really, I again agree with some of the sentiment that this offers an important opportunity for patients to receive a neoadjuvant with a carboplatin-based therapy, and then also to trust the clinicians to be able to withdraw therapy in the event that they're experiencing toxicities.

I also want to mention that adjuvant therapy or maintenance therapy becomes a slippery slope. I know we're talking about phases of research as it applies to the post-surgical, but I also know that that maintenance phase also become slippery in terms of the duration of therapy that a patient would benefit from, so it just lends to making sure that this doesn't come into some type of perpetual type of adjuvant therapy either.

DR. SPRATT: Great points.

Dr. van Berkel?

DR. VAN BERKEL: Thank you. It's Victor van Berkel again. I guess my question perhaps is

more directly relevant to question number 2, but I think it actually bleeds into a little bit of question number 1, and I apologize if this ends up being a bit of an inflammatory question for the FDA. I guess my question is, we're going to say we want trials to look like this, and as a scientist, I understand that we want the best possible data about things. We say we're going to do a 4-arm trial and figure out really what things are going on.

Six years ago, you guys told AstraZeneca, "Okay. We think we would like you to do this," and they didn't, and now we're talking about approving it anyways. The other trial, I don't know if similar discussions were had at that time -- imagine that they were -- and that drug was approved also. So if we say, "Well, you didn't do that, but okay, we're going to approve you anyway," and now we come to question number 2, and we say, "You need to have a 4-arm trial," and they go, "Well, alright," and then 6 years from now, we have another set of data that they don't have a 4-arm

trial and they didn't do that, at what point does your recommendation for what they should do have teeth?

DR. LARKINS: Hi. This is Erin Larkins from FDA. Thank you. That's exactly the point of why this was brought here. As we discussed before, we want exactly what you're giving us, your opinion. You'll notice we didn't ask a risk-positive/ risk-benefit question. We want it to be discussed what you think is reasonable, is there a risk-benefit, and that's your purview for discussion, and we want to hear that opinion. But we've tried to separate out data in hand, which you're dealing with here, and future, and that's the point.

At the time we didn't have any IO data. We didn't know what IO or any of these would do in this setting, so we didn't have a strong scientific safety argument to say we're going to put your study on hold if you don't do a 3-arm study design. We feel now that we do have enough data generated to say that this is really not the best approach to

continue taking.

That's a large part of what the second discussion is for, is to say do you think we should have more teeth to say we're potentially going to put a study on hold because you can't meet stated objectives if you do a 2-arm study design? Because your stated objective should really be to prove that both parts of the regimen are having an effect.

To be clear, in an ideal world, do we love a forum study design with formal comparisons between each arm so that we can say exactly where the benefit is? Yes, but we realize that's not realistic. We are open to discussions with companies, as we were at that time for 3-arm study design proposals, proposals for prespecified descriptive comparisons between the two experimental arms. That's where a big part of the upsizing comes in these trials because you're not expecting, necessarily, a massive difference between, say, neoadjuvant only and a perioperative regimen when you're adding them together. Maybe

you're expecting an incremental bump.

We are open to discussions on whether a descriptive analysis would be fine. We don't want to let the perfect --

DR. SPRATT: Be the enemy of good.

DR. LARKINS: -- thank you. Yes. I was trying to remember the phrase. We feel that having some information on this will be helpful in making approval decisions.

I also was very happy to hear Dr. Spratt bring up PACIFIC-2 because this was an issue that came out at our FDA public workshop as well. There does get to a point when you're adding things, where the toxicity probably outbalances the benefit. I actually feel that this is a risk mitigation and protective strategy for both patients enrolling in trials and companies going forward to potentially have a neoadjuvant-only arm.

It could be quite possible that you're seeing a really great benefit by adding a new drug on to, say, a perioperative IO backbone, but when you then try to give a little more in the adjuvant,

maybe that's too much, maybe that doesn't do enough. And we've seen this in not just PACIFIC-2. There was another study in the concurrent chemoradiation setting that had the same exact outcome, where they tried to add the IO to both the concurrent chemo RT phase and after, and it did not look better than just giving it after.

So to your point, Dr. van Berkel, that's sort of why we're here, is to say, should we have a little more weight behind us to say, "Look, we really don't think we can keep doing this going forward. It's just going to create more of a mess."

DR. SPRATT: And to layer on challenging -- this is Dan Spratt -- the FDA, for industry, if EFS is a sufficient endpoint, assuming there's not worsening of survival, looking at the CheckMate trial with just neoadjuvant, a very small trial, wildly positive, and the AEGEAN trial, those p-values of the primary endpoint were insanely positive. It didn't, in hindsight, need to be as large. Probably the total sample size required may

be smaller.

Dr. Conaway?

DR. CONAWAY: I was sort of hoping for more discussion. I really haven't formalized this in my head. There are so many difficult issues circulating, so I'll try and make this somewhat comprehensible. We're talking about precedent for this, and someone made the point this is dosing, and there is precedent for taking drugs back to look at alternative doses before moving forward. So I think that saying, "Oh, well, this is never done, or these other drugs have been approved," there is precedent for looking at other options for dosing.

Looking at the data, I think, yes, we cannot separate out the effective phases, but looking at the effect on the short-term outcomes, if I were a betting man, I'd be betting that most of the action is in the neoadjuvant setting. So I think that's an important thing to explore for all the reasons we said, that the adjuvant may just be adding toxicity with no benefit. And at the end of the

day, we just don't know; and I have some sympathy for the FDA trying to make a decision about risk-benefit when we honestly don't know the benefit. We do know some of the risks of the adjuvant, but we don't know the benefit.

So I still haven't quite said in my mind what I think the ultimate answer is about the prior to approval phrase in that question, but these are the issues that I'm thinking about.

DR. SPRATT: Thank you.

Dr. Kunz?

DR. KUNZ: Pam Kunz. I'm reflecting on what's all been said and lots of great discussion, and the fact that this is incredibly complicated. I think there are multiple truths here. There's a truth that the AZ study met its primary endpoint. There's a truth that it's incredibly muddy in terms of what to actually offer patients in terms of neoadjuvant, adjuvant, and/or perioperative, and I think in terms of this discussion point at hand, I wonder if there's an intermediary kind of question.

We're asked whether an additional trial

should be conducted, and I'm wondering if we should be thinking about -- I know we'll in the future talk about what to do moving forward, but for the existing trials like AEGEAN that's just completed, is there a way for us to think about what other, perhaps, simple question could be asked?

We talked about pragmatic trials. Is there something along the lines of the accelerated drug approval process where a confirmatory trial is required, but for trials that are either in progress or have just been completed but don't quite meet this new bar that we're talking about, we can do something in a simpler way where we perhaps say, yes, we don't want to waste the work that's been done. We want durvalumab to be available to patients, but we're really going to require something that confirms.

DR. SPRATT: And ideally -- Dan Spratt -- applied to all companies as well. With pembro, while perioperative, with all the flaws we've discussed, looked better than adjuvant, it still doesn't answer the question to neoadjuvant.

Alright. Dr. Advani?

DR. ADVANI: This is Ranjana Advani. I had a similar thought, what Pam just brought up, about can we find an intermediary. This trial met its endpoint, and it's hard to take that away. In hindsight, yes, the design wasn't rigorous and doesn't answer, and moving forward, things need to be different, but can we require that there be longer term follow-up mandated for the toxicity part of it, at least, so that companies are forced to actually report that very rigorously? Not just like it's met, and 5 years and we're done, no, but substantially more time so that at least we can say with fair conscience, then, that it's not doing more harm and that things have settled down. Thank you.

DR. SPRATT: Thank you.

Dr. Frenkl?

DR. FRENKL: Thank you. I wanted to go back a little bit and comment on what you were saying, Dr. van Berkel, about FDA told you to do this. I just want to give a little bit more background on

how industry approaches the FDA meetings and the advice that we get. From an industry perspective, we request these meetings and really value obtaining the FDA feedback, and the goal is to reach an agreement with the FDA about a trial design that would eventually be approvable so we could get the drug to patients should it work.

So speaking from my experience only -- and I've worked in three large pharmas now -- I've never really experienced a situation where FDA clearly says we object to this design, don't do it, it won't result in approval, and then we would move forward. Again, our goal is to reach some type of an agreement with you so that it would work.

So I don't question the FDA -- and I probably experienced it actually in some of my past experiences -- where they said the contribution of phases cannot be addressed and that alternative design options could be continued; however, then there's the context of the implication of this.

In Appendix 9 here, the applicant actually provides it, where the implication is that the

label on this study would need to specify that both neoadjuvant and adjuvant therapy are necessary to provide the clinical benefit. So that's the implication, and that's what we as industry would decide, is that what we can live with, or if we really wanted a neoadjuvant and a separate adjuvant indication, then we would perhaps proceed with the longer 2-arm trial.

So that was the context back then with the data. And I understand that things evolve and change, but it's not that we're like blatantly saying, "Okay. FDA said this, but we don't care. We're moving forward with our idea, and we just don't want to do this bigger study." It's much more complex, and we take it all into consideration.

DR. SPRATT: Thank you. It's Dan Spratt. So there'something I think is relevant to this discussion. First of all, I agree with many of the comments. This is a floridly positive trial, and I think it's challenging, as we hear. When you're designing a trial, people will say skate to where

the puck is going. Well, you can't necessarily in 2018 know what's going to be today, so you have to design a trial and put massive amounts of resources into it. I think there are clinically meaningful benefits to patients with this regimen, and as we've said, it's probably going to come down to the art of medicine.

I think the BR.31 trial, as well as a lot of the data shown, the adjuvant phase seems -- and I think it was said by some of the people today, maybe it provides some benefit in some patients, but it's unclear who, but future trials hopefully will establish this.

So I guess to the question at hand here, I think this is going to be something that gets sorted out after approval, and would be, in my opinion, the appropriate stance. But the problem with that, just to be clear -- and I mentioned this previously -- as a prostate cancer oncologist, the duration of hormone therapies established in the 1970s, we still today, 50 years later, have gone from lifelong, to 36 months, to 18 months, and now

we have trials of 12 months, and still, it is very hard to run noninferiority trials. Industry has no incentive to actually run those trials, so there's a lot of burden, and we've seen a lot of morbidity to patients, but this is a very lethal disease, and these patients need options.

The one other comment I would make, and we'll say tangentially related, I am surprised by such an aggressive and lethal disease. While I'm not a thoracic oncologist, the endpoints for approval in this setting, looking back at the FDA's history, DFS was established over a decade ago, two decades ago, and with individual patient data, had an R-squared for overall survival of 0.99 in radiotherapy trials with chemotherapy.

When you look at all these immunotherapy trials, EFS correlation to OS treatment effect is 0.27. So again, the bar has been set, but it is something very surprising to me that we have many trials now that don't show quantity-of-life benefits, not survival benefits, and there's not quality-of-life benefits, but we're saying there

are benefits. Again, we hear from patients that these are meaningful benefits, but it is just something in this era. Are these endpoints the right endpoints, and if path CR is so important, you can only do that in a neoadjuvant setting. I don't know if anyone has comments on that, but these seem like very soft endpoints for such a lethal disease, in my opinion.

Go for it, Ravi.

DR. MADAN: Ravi Madan, NCI. I mean, just to piggyback on that a little bit, because I'm also not a lung cancer specialist, but EFS, really, has been established in this, but is that right? Because another way to look at this is -- and this is beyond the scope of this question but very much in line with, I think, what you're thinking here -- is it better to get adjuvant therapy or is it better to get sequential therapy at recurrence? But you can't really ask that question because of the established endpoints and things. So I do think that some imagination as we move forward, now that we have therapies that work, will be a benefit

for industry and patients alike.

DR. SPRATT: Any other discussion comments? I think this has been a good discussion.

(No response.)

DR. SPRATT: I will summarize the discussion. I will try.

I think to summarize a lot of the discussion, the AEGEAN trial demonstrated that perioperative durvalumab met its primary endpoints, improved path CR and EFS. While not meeting the prespecified p-value threshold for DFS, it's pretty dang close. I think OS is clearly not worse, and we'll see over time the events increase over time, but I will say it's a small relative and absolute difference on survival.

But ultimately why we're here is that we can't necessarily clearly assign -- and I think even the applicant, as well as the FDA, and like all of us have said, we can't clarify the contribution of each phase. It's very clear from the trial that neoadjuvant had effect. We looked at some of these endpoints. The path CR rates,

there is effect. It's unclear what the adjuvant effect is. It seems that the side effect profile, most would say it's very tolerable, well received. We heard from patients that were on a similar, I guess, type of regimen that it was annoying. It wasn't devastating.

People did bring up it was about 1.5 percent versus less than a percent of patients in each arm, and the adjuvant phase did have mortality events, that that still is relevant. And some of the chronic lower grade side effects may still be clinically meaningful, and we don't know. Obviously, when you're talking about kidney disease or diabetes, those can have multiyear chronic effects.

I think many of the panel members discussed that this is an important regimen that should be available to patients, and it's something that we can optimize going forward to who should have it for how long. I think others brought up, we'll say, disappointment that this wasn't addressed initially upon discussion with the FDA as a

recommendation, but also that maybe that discussion is not always as crystal clear as do this, or else.

I think that many of the panel members think that we need answers, though, to this question probably sooner than later, and that there are suboptimal consequences once a regimen's approved, and that it is not simple to go back to optimize sequencing or duration.

If there are no further questions or comments, we will now proceed to question 2, which is a voting question. We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing, and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the

vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to. We will continue in the same manner until all questions have been answered or discussed.

Question 2 is, should the FDA require that new trial design proposals for perioperative regimens for resectable non-small cell lung cancer include adequate within-trial assessment of contribution of treatment phase?

Are there any questions to the wording of the question.

Jim?

MR. PANTELAS: Is there a reason why we're limiting this to non-small cell lung cancer?

DR. SPRATT: I'll go to the FDA for that.

DR. PAZDUR: Because that's how people were cleared, okay?

(Laughter.)

DR. KLUETZ: This is Paul Kluetz. I would

say that this is obviously a situation that's relevant across resectable disease that has neoadjuvant and adjuvant components, but the question should be answered as it is stated, with respect to non-small cell lung cancer, given that's what we've been talking about today.

DR. PAZDUR: There are issues on clearance of people in other discussions, so that's why we're focusing it on a specific disease.

DR. SPRATT: That was Dr. Pazdur talking.

Any other questions on the wording?

Dr. Rosko?

DR. ROSKO: Ashley Rosko. I just want to be crystal clear, because it's saying they require that new trial designs. The AEGEAN, the study that we're discussing, is an existing trial. This is about future trials.

DR. LARKINS: Correct.

DR. ROSKO: I just want to be a hundred percent clear that we're all discussing future clinical trials.

DR. LARKINS: Yes. This is Erin Larkins,

FDA. This is not for studies that are fully enrolled and about to read out next week. This is for what we're dealing with right now, which is sponsors coming to us with new trial designs to add on in this space.

DR. SPRATT: Any other clarifications to the wording?

(No response.)

DR. SPRATT: Okay.

If there are no further questions concerning the wording of the question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. FRENKL: Could I ask a process question? In the past, there's been a discussion --

DR. SPRATT: State your name, please.

DR. FRENKL: -- before the vote.

DR. SPRATT: State your name so people know that you have questions on how to vote.

DR. FRENKL: I'm sorry, Tara Frenkl, industry rep. I am non-voting, but the way the agenda was, and in the past, there was a discussion before the vote. Is that different in this session than the past?

DR. SPRATT: You'll able, for voting members, to then explain and clarify why you voted the way you voted after the vote.

DR. FRENKL: Thank you.

DR. SPRATT: Takyiah Stevenson, DFO. For the record, there are 11 yeses, 0 noes, and 0 abstentions. Thank you.

DR. SPRATT: Now that the vote is complete, we will go around the table and have everyone who voted state their name and vote, and if you want to, you can state the reason why you voted as you did into the record.

Mr. Mitchell, can you go first?

MR. MITCHELL: I can. I'm David Mitchell. I voted yes. I think that we need to know, in a situation like this, which phase of treatment is contributing what. And especially, the thought of giving patients a year of adjuvant therapy with the risks involved, the toxicities involved, continued treatment for that length of time not knowing if it's doing any good whatsoever, is not acceptable, I think, for patients.

So I believe that in the future, the FDA should be requiring that we have study designs that will answer the question so we're making sure that we're giving people treatments that are safe and effective, but also making sure that they're needed; that they're doing good; that patients are not being subjected to a long period of time with treatment that isn't necessarily helping them at all.

DR. SPRATT: Thank you so much.

Dr. Madan?

DR. MADAN: Ravi Madan, National Cancer Institute. We struggle with this dilemma here

because of, actually, the success in the field over the last several years, and that's a credit to industry, it's a credit to the investigators, and it's of great benefit to patients. But with that success, now comes the complicated path about how to move forward. Things are going to be harder now because we have more therapies, and this consideration here is very important in that regard.

I think that it's going to be more complicated when we move forward because not only are there more therapies, but likely they're not going to be as well tolerated as the immune checkpoint inhibitor, and the mortality issues are going to be higher than the 1 percent we talked about today.

But I also think there are different ways to approach this. There are more ways to use vision and imagination, and the only path isn't a phase 3 with an extra 2 arms and an extra 1500 patients; the other path is a more deliberate preregistration approach, whether it's preclinical or phase 2

trials with rich correlatives, that can better inform a phase 3 such that you move forward focused on either neoadjuvant or adjuvant with a well-informed rationale. I think that's something that we lost sight of a little bit in this conversation, but it's another way to refocus on getting the answers that, really, patients deserve when they embark on a therapy. Thank you.

DR. SPRATT: And, Dr. Madan, can you state what your vote was?

DR. MADAN: Oh, sorry.

DR. SPRATT: Sorry.

DR. MADAN: I voted yes. My apologies.

DR. SPRATT: Dr. Conaway?

DR. CONAWAY: Mark Conaway, University of Virginia. I voted yes because from the discussion, I think we'd all agree it's an important question that needs to be addressed and I'd say understanding the challenges. Future trials will be essentially trying to establish superiority, and to some extent noninferiority, all within the same trial. But having said that, I think the point was

made that having some information is infinitely better than no information at all, so I think the trials do need to collect the contribution of phase information.

DR. SPRATT: Thank you. Dan Spratt. I voted yes I think for all the reasons stated previously. I think this is very challenging to answer after the fact the optimal sequencing. I would say, as I mentioned earlier, I think duration is probably equally, if not more, important here, especially when we don't have proven interaction of the event and sequencing; so I think the questions of duration, why even 1 year, or in some diseases 2 years or 6 months, and where this is coming from for the exact same reasons.

I would also like to say that when you look at the trial portfolio that was put up -- which is very impressive -- from just AZ, let alone many companies, there are a lot of trials going on in diseases like non-small cell lung cancer. So I don't agree that this is not a feasible option to be done, but if it's not a requirement, it's

probably just not going to be done. Thank you.

Dr. Kunz?

DR. KUNZ: Pam Kunz. I voted yes. I, again, agree with all that's been stated, and I think that moving forward, my hope is that we eliminate some of this ambiguity with the patient physician conversations. I think it's a big burden to put on patients to have them make the decision, and I think that more is not always more. We really owe it to our patients to provide them with some of that clarity and really provide them with that high-level evidence. I would also hope, though -- Jim raised this around does this apply to other cancers. As a GI oncologist, where this for sure applies, I hope that the FDA considers this conversation in other solid tumors.

As a final comment, I think that as we think about requiring this for future, we also, I think as Dr. Madan stated, really need to think about not slowing down the process and making it more inefficient; so are there ways that we can, really, I think raise our own bar, but really increase

efficiency as we do it? Thank you.

DR. SPRATT: Thank you.

Jim Pantelas?

MR. PANTELAS: This is Jim Pantelas. I voted yes. The only thing that I would add to all of this is the consideration that less can be more; that maybe we're trying to accomplish too much out of one trial, and maybe what we're looking at here is three that could run consecutively with smaller ends on each. There are other ways of doing this, but I think we need another way.

DR. SPRATT: Thank you.

Dr. Advani?

DR. ADVANI: Ranjana Advani. I voted yes for most of the reasons already stated. I do think it's an important question, and in hindsight, what happened, happened, and we're moving forward. I really hope that you'll apply to all tumors, not just this case and example, but also the question of having testing the shorter maintenance versus longer, but also considering some novel endpoints. One was the pathological CR, but it's not used for

many things.

But circulating to AEGEAN, especially in lung cancers, showing a lot of promising results, I wonder if there's an opportunity to use some of those metrics to define so that trials can be read out a little faster to see if they're meaningful. Thank you.

DR. SPRATT: Thank you.

Dr. Lieu?

DR. LIEU: This is Chris Lieu, University of Colorado. I voted yes. I, obviously, agree with all the comments. I'll use the extremes here. We have an easy, non-toxic drug that we just give a little bit on both sides; that's one end of the spectrum. The perioperative therapy in that setting doesn't really require additional data, but the problem is that we don't know what's coming down the pipeline.

In fact, we probably actually do. There are some cellular therapies that are coming down the pipeline that are incredibly toxic and very hard to give, and that's the end of the spectrum that I

think we're all worried about, that if we don't answer this question upfront, then we're left just creating a ton of toxicity with potentially very effective therapeutics but are incredibly difficult to give and sometimes to tolerate, and then we're going to be left with not answering this question. We have to answer this question now.

Now, I would make the point -- because this is not a subtle thing -- that as a group, we're going to cost a lot of millions of dollars by making this decision and potentially delaying drug development. So to Dr. Kunz and Dr. Madan's point, and to Dr. Advani's point, we have to find better surrogate markers, particularly in this space. It might be ctDNA, it might be better readout on path CR, but that is an incredible amount of work, as we saw from the multiple myeloma group when they presented to this committee in April. But it is incumbent upon this group and industry to work together to find those surrogate endpoints because otherwise, we're going to start delaying drug approvals by 5-6 years.

DR. SPRATT: Thank you so much.

Dr. Rosko?

DR. ROSKO: Ashley Rosko. I voted yes. I think looking forward, I really want to focus on the fact of the type of patients that get enrolled into neoadjuvant studies versus the type of patients that get enrolled into adjuvant is really being able to better characterize the health of those patients in terms of their overall fitness or frailty. I worry about the types of patients and selecting out for patients that are more fit to be able to benefit from a type of neoadjuvant therapy, whether it's in this setting or other disease settings, and really urge the FDA to be able to support fitness and frailty metrics that are embedded into clinical trial design.

Health-related, quality-of-life metrics that were provided here are not quite the same thing in terms of being able to measure trajectories over time, and I really urge, that way we are able to better characterize the type of patient that is actually able to receive the therapy that's

indicated.

DR. SPRATT: Thank you.

Dr. Ghafoor?

DR. GHAFOOR: Hi. My name is Azam Ghafoor from NCI. I agree. I think we need to clarify this question. I think, really, we need to determine the design studies that actually look at the adjuvant setting in the perioperative setting, if that's really the focus here. We know from prior trials that the induction chemoimmunotherapy, neoadjuvant, has very strong data, especially Patrick Ford's data. You can downsize tumors, more R0 sections. I think really the question here is whether we can design trials that clarify the adjuvant setting so we don't commit patients to unnecessary year-long immunotherapy.

So that's my stance. I think incorporating biomarkers will be important. We know from other trials, early clearance of ctDNA, as mentioned before, pathological CR, can have a profound effect on EFS. I think incorporating those in the trials -- and going back, it may not have to be a

4-arm trial, but going to a 3-arm trial and excluding the purely adjuvant setting so you get a better clear readout of the perioperative setting.

DR. SPRATT: Dr. Ghafoor, can you just state what your vote was?

DR. GHAFOOR: Yes.

DR. SPRATT: Thank you.

DR. GHAFOOR: I voted yes.

DR. SPRATT: Sorry. Thank you so much.

Dr. van Berkel?

DR. VAN BERKEL: This is Victor van Berkel, and I voted yes. As a clinician and as a scientist, my life is often in quite a bit of tension. As a scientist, I want the cleanest data possible that will give me the best answer for a question, rather as a clinician, I want to fix the person in front of me today and not have to wait for 6 years to get a perfect trial done. I understand that is the conflict that arises throughout all of clinical trials.

I do think that having a more rigorous requirement for these trials is going to make

things more complicated, more expensive, and take longer. I understand all of those things. I think to echo what Dr. Larkins and both Dr. Spratt said, I think that increased rigor may actually behoove the companies that are doing it because they may find applications that they were not expecting that will be used by more patients in the long run, so I think that there is potential benefit there as well.

DR. SPRATT: Thank you so much.

While not a voting member, Dr. Frenkl, if there are any comments you'd like to add on, we shall allow.

DR. FRENKL: Why, thank you very much.

Thanks. Tara Frenkl. I think it can be challenging to have a blanket statement about this, and many of you mentioned take into account the mechanism of action, the safety, the disease course itself, and what else is out there. I do think that moving forward, it's going to be really important to have industry as part of this conversation as we're talking about the trial

designs, as well as medical experts, so we can really focus on where the value is for the patient when we're designing this, and trying to come up with new surrogate endpoints that would help the trials read out faster.

I do still have concerns, a lot, about the feasibility of these studies, and I think it is a little bit underestimated here, so really understanding the difference between the perioperative arm and the adjuvant, and the neoadjuvant arm and that contribution. Even though it's descriptive, really trying to understand what that is, is going to be critically important to us as we make decisions on how we spend our resources as well. Then the whole timeframe, I think 6 years is actually a little bit optimistic as well, and it's probably going to be somewhere closer to 8 to 10 to have these trials read down. I don't want to slow down drug development for patients either. So just a lot to consider, and I think the conversation needs to continue, so thanks so much.

DR. SPRATT: Thank you.

So to summarize, there were unanimous votes for yes, that this should be something factored into new trial designs to better understand the contribution of phase. I think the panel generally agrees that this is something, ideally, that can be addressed upfront; ideally, that it is harder to address after the fact. Comments were made that it probably extends beyond simply sequence or phase, as well as duration of therapy.

There were multiple comments made about that this will increase cost of drug development, potentially time as well, potentially complexity, but that, overall, the value may be substantial, especially to patients, and that less sometimes may be more. I think that probably, in lung cancer where it's a common disease, if we're only focused on that, it may be something far more feasible, especially if this extends -- while many made comments -- outside to other solid tumors and rare diseases, and that becomes its own separate challenge. But overall, there was strong consensus that this is an important thing to mandate or

figure out how best to incorporate into future trial designs.

So before we adjourn, are there any last comments from the FDA?

DR. LARKINS: Hi. This is Erin Larkins from FDA. We just wanted to thank the advisory committee for all your excellent discussion today and feedback, which we'll take under consideration. And as always, we want to thank the public, the open public hearing speakers, for their input, as well as all the investigators and the patients who participate on clinical trials and the sponsors that run them.

We want to advance patient care as much as the next person. A lot of us have seen patients ourselves for many, many years, so we're not coming at this from just an academic perspective either. So we just want to acknowledge everything that goes into all of these trials being conducted, and that the ultimate end we want is benefit for patients. Thank you.

DR. SPRATT: Dr. Pazdur, you had brought

up -- real quick -- you wanted to get people's thoughts on the formatting of the point/ counterpoint.

DR. PAZDUR: Yes. We used the unified briefing document, and I just wondered, again, how people felt, the use of that versus having two separate briefing documents, if people could comment on that. Is it a unanimous vote, the briefing document being one --

DR. SPRATT: Yes, it was quite helpful.

DR. PAZDUR: -- rather than having -- okay. Thank you.

Adjournment

DR. SPRATT: I did want to take the time to thank the FDA, AstraZeneca, the public, the OPH presenters, the panel, and of course all the patients that enrolled on this practice-changing trial. Thank you so much. We will now adjourn the meeting. Thank you, everyone.

(Whereupon, at 1:49 p.m., the meeting was adjourned.)