FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Virtual Meeting

Friday, September 23, 2022

9:00 a.m. to 1:37 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

She-Chia Chen, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Jorge A. Garcia, MD, FACP

(Chairperson)

Chief, Division of Solid Tumor Oncology

George & Edith Richman Distinguished

Scientist Chair

Professor of Medicine and Urology

GU Medical Oncology Program

University Hospitals Seidman Cancer Center

Case Comprehensive Cancer Center

Case Western Reserve University

Cleveland, Ohio

Ranjana H. Advani, MD

(September 23 only)

Saul A. Rosenberg Professor of Lymphoma

Division of Oncology

Stanford University School of Medicine

Stanford, California

Christopher H. Lieu, MD

Associate Professor of Medicine

Associate Director for Clinical Research

co-Director, Gastrointestinal Medical Oncology

University of Colorado Cancer Center

Aurora, Colorado

Ravi A. Madan, MD

Senior Clinician, Genitourinary Malignancies Branch

Head, Prostate Cancer Clinical Research Section

Program Director, Physician-Scientist Early Investigator Program

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National Cancer Institute, National Institutes of Health

Bethesda, Maryland

David E. Mitchell

(Consumer Representative)

Founder, Patients for Affordable Drugs

Bethesda, Maryland

Jorge J. Nieva, MD

(September 22 PM session and September 23 only)

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University of Southern California (USC) Norris Comprehensive Cancer Center

Keck School of Medicine of USC

Los Angeles, California

ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE

(Non-Voting)

Albert L. Kraus, PhD

(Acting Industry Representative)

Global Regulatory Portfolio Lead – Oncology

Pfizer, Inc.

Guilford, Connecticut

TEMPORARY MEMBERS (Voting)

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(September 22 PM session and September 23 only)

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Oregon Health & Science University

Portland, Oregon

Stephanie Y. Crawford, PhD, MPH

(September 22 PM session and September 23 only)

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Professor, Department of Pharmacy Systems, Outcomes and Policy

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(September 22 PM session and September 23 only)

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Director (Acting)

Office of Oncologic Diseases (OOD)

Office of New Drugs (OND), CDER, FDA

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Nicole Gormley, MD

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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

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

My name is Jorge Garcia, and I will be chairing today's meeting. I will now call the last session of the September 22-23, 2022 meeting of the Oncology Drug Advisory Committee to order. Dr. She-Chia Chen is the designated federal officer for this meeting and will begin with introductions.

Dr. Chen?

Introduction of Committee

DR. S. CHEN: Thank you, Dr. Garcia.

Good morning. My name is She-Chia Chen, and I am the designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation. We'll first start with ODAC members.

Dr. Advani?

DR. ADVANI: Dr. Advani, Stanford.

DR. S. CHEN: Dr. Garcia?

DR. GARCIA: Jorge Garcia, GU medical oncology and the chair of the Solid Tumor Oncology program at University Hospitals Seidman Cancer Center, Case Western Reserve University in Cleveland, Ohio.

DR. S. CHEN: Dr. Lieu?

DR. LIEU: Good morning, everybody. My name is Chris Lieu. I'm a GI medical oncologist and associate director for clinical research at University of Colorado Cancer Center.

DR. S. CHEN: Dr. Madan?

DR. MADAN: Good morning. Ravi Madan, head of the prostate clinical research section at the National Cancer Institute.

DR. S. CHEN: Mr. Mitchell?

MR. MITCHELL: Hi. I'm David Mitchell. I am president of Patients for Affordable Drugs.

DR. S. CHEN: Dr. Nieva?

DR. NIEVA: Jorge Nieva, Section Head, Solid

Tumors, University of Southern California and Norris Comprehensive Cancer Center, and the Keck School of Medicine at USC.

DR. S. CHEN: Dr. Chen?

DR. A. CHEN: Andy Chen, Oregon Health & Science University.

DR. S. CHEN: Dr. Crawford?

DR. CRAWFORD: Good morning. Stephanie Crawford. I'm professor in the Department of Pharmacy Systems, Outcomes and Policy, University of Illinois Chicago, and I'm also executive associate dean for Faculty Affairs and Strategic Initiatives in the College of Pharmacy, and my area of expertise is drug safety and health equity in the medication use process.

DR. S. CHEN: Dr. Freidlin?

DR. FREIDLIN: Good morning. Boris Freidlin. I am chief of the biostatistics branch in the Division of Cancer Treatment & Diagnosis, National Cancer Institute.

DR. S. CHEN: Dr. Harrington?

DR. HARRINGTON: Good morning. David

Harrington, biostatistician, Dana-Farber Cancer Institute and Harvard School of Public Health.

DR. S. CHEN: Ms. Nadeem-Baker?

MS. NADEEM-BAKER: Good morning. I'm Michele Nadeem-Baker. I am a cancer patient, and I head a few patient support groups and communities online.

DR. S. CHEN: And Dr. Sekeres?

DR. SEKERES: Good morning, everyone. This is Mikkael Sekeres, professor of medicine, chief of Division of Hematology at the Sylvester Cancer Center at University of Miami, former standing member and chair of ODAC.

DR. S. CHEN: Next is acting industry representative to the committee.

Dr. Kraus?

DR. KRAUS: Yes. Hi, everyone. Albert Kraus. I'm an experienced drug developer who's been involved in research and development of cancer medicines for multiple decades, with multiple companies, and I hope to bring that perspective to any discussion. I am currently employed by Pfizer.

Thank you.

DR. S. CHEN: Finally, I would like to introduce FDA participants.

Dr. Pazdur?

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

DR. S. CHEN: Dr. Theoret?

DR. THEORET: Yes. Hi. My name is Marc Theoret, oncologist. I'm a deputy center director of the Oncology Center of Excellence.

DR. S. CHEN: Dr. Gormley?

DR. GORMLEY: Good morning. I'm Nicole Gormley. I'm a hematologist and the director of the Division of Hematologic Malignancies II, at the FDA.

DR. S. CHEN: Dr. Richardson?

DR. RICHARDSON: Hi. Nicholas Richardson, clinical team leader, Division of Hematologic Malignancies II, at the FDA.

DR. S. CHEN: And Dr. Telaraja?

DR. TELARAJA: Hi. I'm Deepti Telaraja, a

clinical reviewer in the Division of Hematologic Malignancies II, at the FDA.

DR. S. CHEN: Thank you all.

DR. GARCIA: For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption.

Thus, a gentle reminder; individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory 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 topic during the break. Thank you.

Dr. She-Chia Chen will now read the Conflict of Interest Statement for the meeting.

Dr. Chen?

Conflict of Interest Statement

DR. CHEN: Thank you, Dr. Garcia.

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

The following information on the status of this committee's compliance with federal ethics and

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

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

Related to the 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 purpose 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

For today's discussion, the committee will hear an update on new drug application, NDA, 211155, for Copiktra, duvelisib, capsule, submitted by Secura Bio, Inc. This product was approved under Section 505(b) of federal Food, Drug, and Cosmetic Act, FD&C Act, for use in the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma after at least 2 prior therapies.

The update includes the final overall survival data from the DUO trial, IPI-145-07, submitted in response to postmarketing requirement 3494-3 detailed in the September 24, 2008 [sic 2018] approval letter, available at www.accessdata.fda.gov/drugsatfda-docs/appletter/

2018/211155Orig2s000ltr.pdf. Based on the updated overall survival information along with the safety data with duvelisib, the committee will discuss a current assessment of benefit-risk. This is a particular matters meeting during which specific matters related to Secura Bio's NDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208 (b)(3) to Dr. Andy Chen.

Dr. Chen's waiver involves his employer's research contract for two studies funded by competing firms. One study is funded by TG Therapeutics, and Dr. Chen's employer received between $0 and $50,000 per year. The second study is funded by Fate Therapeutics, and Dr. Chen's employer received between $0 and $10,000 per year.

The waivers allow this individual to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in

the waiver documents, which are posted on FDA's website at www.fda.gov/advisory-committees/committees-and-meeting-materials/human-drug-advisory-committees.

Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Division, 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

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

We would like to remind members and

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

DR. GARCIA: Thank you, Dr. Chen.

We will now proceed with the FDA introductory comments from Dr. Nicholas Richardson.

Dr. Richardson?

FDA Introductory Comments – Nicholas Richardson

DR. RICHARDSON: Good morning, and welcome to the September 23rd Oncologic Drugs Advisory Committee meeting. I am Nicholas Richardson, a pediatric hematologist/oncologist in the Division of Hematologic Malignancies II, at the FDA. I will provide a brief introduction for duvelisib in patients with chronic lymphocytic leukemia and

small lymphocytic lymphoma, and the issues under discussion.

Today's ODAC will focus on a current assessment of benefit-risk for duvelisib in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma. The issues under discussion include updated overall survival data from the randomized DUO trial, evaluating duvelisib versus ofatumumab in patients with relapsed or refractory CLL or SLL, which supported the initial approval of duvelisib.

The 5-year OS analysis from the DUO trial showed a potential detriment in overall survival. The potential detriment is in the setting of a benefit in progression-free survival and overall response rate, which indicates that the potential OS detriment is a primary safety concern.

Within the DUO trial, duvelisib also demonstrated substantial toxicity with higher rates of death due to adverse events, grade 3 or greater toxicity, and serious adverse events compared to the control arm, along with high rates of treatment

modifications, indicating tolerability concerns. Because of the OS findings and the toxicity data, there are concerns regarding the selected dose of duvelisib.

Finally, the updated data from the DUO trial will be placed in the context of the concerns with the PI3K inhibitor drug class, which was discussed at the April 20, 2022 ODAC, and highlighted the importance of overall survival in informing benefit-risk, especially in patients with indolent diseases, such as CLL or SLL, that have a long natural history, multiple available therapies, and the potential for prolonged survival. Taken together, we are asking the committee today to discuss a current assessment of benefit-risk for duvelisib.

I'd like to take a moment and highlight some important considerations regarding the mechanism of action of duvelisib. Overactivation of the PI3-kinase pathway is common in cancer, including hematologic malignancies such as CLL. Duvelisib is a PI3K delta and gamma inhibitor and is a targeted

immunomodulatory drug. The delta and gamma isoforms are preferentially expressed in immune cells, particularly leukocytes.

Because of this, duvelisib has a distinct safety profile that includes infections, cytopenias, and immune-mediated toxicities. Infections include pneumonia, opportunistic infections like PCP and CMV reactivation; and with regards to the immune-mediated toxicities, the PI3K isoforms are important for regulatory T-cell function, and the immune modulation leads to the development of immune-mediated toxicities such as hepatitis, pneumonitis, colitis, and rash.

Duvelisib received regular approval in September 2018 for patients with relapsed or refractory CLL or SLL after at least 2 prior therapies. Approval was based on the DUO trial, a randomized, actively-controlled trial evaluating duvelisib versus ofatumumab in 319 adults with CLL or SLL after at least one prior therapy.

The DUO trial excluded patients with prior exposure to a BTK inhibitor. The primary endpoint

was progression-free survival per an independent review committee. Key secondary endpoints included overall response rate and overall survival. Of note, patients with confirmed disease progression were able to crossover to the alternative treatment arm. Approval was based on a demonstrated benefit in PFS and overall response rate. At the time of the initial approval, overall survival was immature with a median of 24 months of OS follow-up.

At the time of the initial approval, several measures were included to mitigate risk. Duvelisib's labeling included a boxed warning for fatal or serious infection, diarrhea or colitis, rash, and pneumonitis. Additionally, the toxicities of neutropenia and hepatotoxicity were included as warnings and precautions.

A risk evaluation and mitigation strategy, or REMS, was also included with the initial approval of duvelisib to ensure its safe and effective use and that its benefits outweigh its risks. Importantly, two postmarketing requirements were issued because of the concerns with fatal and

serious toxicity with duvelisib. One was to characterize longer term safety, and the other was to provide updated overall survival data with 5 years of OS follow-up in the DUO trial.

The 5-year OS data from the DUO trial demonstrate the potential detriment in overall survival in patients treated with duvelisib in the ITT population. The median overall survival, as shown in the table, demonstrated an 11-month difference in OS, favoring the ofatumumab arm. There were a higher number of deaths in the duvelisib arm, and the estimated hazard ratio was 1.09.

The potential OS detriment is in the setting of a benefit in PFS and response rate, indicating a primary safety concern. Notably, the ITT population includes patients with at least one prior therapy, whereas the indicated population for duvelisib is those with at least 2 prior therapies.

The potential OS detriment in the 5-year OS analysis is also seen in the indicated population, consistent with the ITT population, with a higher

rate of death in the duvelisib arm and an estimated hazard ratio of 1.06. As mentioned, the potential OS detriment is in the setting of a benefit in PFS and response rate, and the safety review support a primary safety concern. Overall, there were a higher number of deaths in the duvelisib arm, 50 percent versus 44 percent in the ITT population. Notably, there was a higher rate of death due to adverse events with duvelisib, at 15 percent versus 3 percent with ofatumumab. Fatal toxicity with duvelisib was primarily due to infection, with 9 percent experiencing fatal infections.

The DUO trial allowed crossover upon disease progression. A substantial number of patients crossed over from the ofatumumab arm to receive subsequent therapy with duvelisib, a total of 90 patients. This is in contrast to only 9 patients that crossed over from duvelisib to receive subsequent therapy with ofatumumab. Of the 90 patients that received subsequent treatment with duvelisib, 10 percent experienced a fatal toxicity. Again, fatal infections were the most common cause.

The FDA acknowledges that the presence of crossover can make the assessment of overall survival challenging, however, in this case, we have a substantial amount of crossover to receive subsequent therapy with duvelisib, a drug with serious and fatal toxicity, potentially causing harm to the control group and may mask a difference between the treatment arms that would have favored the control arm. Put another way, despite crossover, we are still seeing a signal for a potential detriment in overall survival and the potential for harm with duvelisib.

The updated overall survival data are further reinforced by the safety data in the DUO trial. This graph shows the safety results from the trial. For deaths due to adverse events, grade 3 or greater toxicity, serious adverse events, and treatment modifications due to an adverse event, the rates were notably higher in the duvelisib arm, as indicated by the blue bars in the graph.

The safety results from the DUO trial

demonstrate that the PI3K associated toxicities of an infection and immune-mediated toxicities of diarrhea or colitis, increased AST or ALT, rash, and pneumonitis are driving the differences in safety. As shown in the table, the incidence of grade 3 or greater PI3K-associated toxicities, except neutropenia, are 2 to 3 times or more higher in the duvelisib arm compared to the control arm.

With the updated OS results, along with the safety data with duvelisib, there are concerns with the selected dose of 25 milligrams. The concerns stem from high rates of treatment modification due to adverse events and exposure-response relationships for safety, along with no exposure-response relationship for efficacy. This is preempted by limited dose exploration of doses lower than 25 milligrams, yielding uncertainty regarding the current 25-milligram dose.

A PI3K inhibitor class ODAC was held in April of this year and raised some relevant considerations for our discussion today. This table shows 6 randomized trials evaluating PI3K

inhibitors in patients with CLL or non-Hodgkin lymphoma, including the DUO trial, that show a potential detriment in overall survival.

All of these trials showed a benefit in efficacy outcomes such as PFS and/or response rate, indicating that the potential overall survival detriment is due to safety concerns. Further, each of the trials demonstrated a higher rate of deaths due to adverse events in the PI3K inhibitor-containing arm.

A consistent pattern of a potential detriment in overall survival in multiple randomized trials within a class of drugs is unprecedented in oncology and gives credence to the fact that this is unlikely to be a finding that is due to chance. Furthermore, this occurred in patients with indolent diseases that have a long natural history, an opportunity for prolonged survival, multiple treatment options, and the presence of disease alone isn't necessarily an indication for treatment.

As a result of the assessment of the PI3K

inhibitor class in hematologic malignancies, multiple regulatory actions occurred. The indications for follicular lymphoma were voluntarily withdrawn from the U.S. market for duvelisib, idelalisib, umbralisib. The SLL indication for idelalisib and marginal zone lymphoma indication for umbralisib were also voluntarily withdrawn.

In addition, the supplemental NDA application for copanlisib, for patients with follicular lymphoma and marginal zone lymphoma, based on the CHRONOS-3 trial, was voluntarily withdrawn in December 2021, and the umbralisib application for patients with CLL, based on the UNITY-CLL trial, was voluntarily withdrawn in April 2022.

The PI3K inhibitor ODAC raised similar issues to those under discussion today, including PI3K inhibitor toxicity, concerns regarding dosing, adequate dose exploration, a narrow range between an effective and a toxic dose, and a potential detriment in overall survival in the setting of a

benefit in PFS and response rate. An important aspect that was communicated at the meeting was the importance of overall survival data in informing benefit-risk, and that products should be safe in order to effectively treat patients with cancer.

Following the April ODAC on PI3K inhibitors, the FDA issued a safety alert regarding the updated overall survival data with duvelisib from the DUO trial to inform patients and healthcare providers on the potential risk. The alert also indicated that the information with duvelisib would be further discussed at a public meeting.

We are here today to discuss a current benefit-risk assessment for duvelisib in patients with relapsed or refractory CLL or SLL. To provide context for the discussion today, I'd like to highlight some important considerations. First, we are discussing updated overall survival data, and overall survival has been deemed the paramount endpoint for patients with cancer, as it is an objective measure of clinical benefit.

FDA considers overall survival as an

efficacy and a safety endpoint with the ability to adequately assess for harm. Because of concerns with fatal and serious toxicity with duvelisib, FDA issued a postmarketing requirement for 5-year overall survival data from the DUO trial.

The 5-year OS data from the DUO trial demonstrate a potential detriment in overall survival in the setting of a benefit in PFS and response rate. The safety data support that the potential OS detriment is due to toxicity with higher rates of death due to adverse events, and fatal toxic deaths in some patients that crossed over to receive duvelisib following disease progression.

The updated OS data should be considered along with the existing safety data, demonstrating substantial toxicity and poor tolerability with duvelisib. This is also in conjunction with the concerns regarding the selected dose of duvelisib, the narrow range between an effective and a toxic dose, and limited dose exploration at lower dose levels. Finally, safety data from same-in-class

products should be considered in the current assessment of benefit-risk for duvelisib.

Lastly, I'd like to further highlight the disease setting and the treatment paradigm for patients with CLL and SLL. Today we are discussing data that shows a potential detriment in overall survival in patients with CLL and SLL, indolent diseases that have a long natural history and an opportunity for prolonged survival. Patients require an indication for treatment, and progression or presence of disease isn't necessarily an indication to treat. Also, patients have multiple effective treatment options with known efficacy and safety, and this table shows the FDA-approved therapies for patients with CLL or indolent non-Hodgkin lymphoma.

It is also important to note that the treatment paradigm for patients with CLL has significantly evolved with the approval of targeted therapies such as BTK inhibitors and the bcl-2 inhibitor, venetoclax.

Currently, most patients with CLL or SLL

will be treated with a BTK or bcl-2 inhibitor as part of frontline or second-line therapy. This is relevant to today's discussion because the data with duvelisib does not include patients with prior BTK or bcl-2 inhibitor exposure. The disease setting and available therapies are an important consideration as we discuss a current assessment of benefit-risk for duvelisib and the issues at hand.

For today's ODAC, we would like the committee to discuss the benefit-risk profile of duvelisib for the currently indicated population, considering the updated results of the DUO trial. The voting question is, given the potential detriment in overall survival, duvelisib-associated toxicity, concerns with the selected dose, and the safety issues with the PI3K inhibitor class, is the benefit-risk profile of duvelisib favorable in patients with relapsed or refractory CLL or SLL after at least 2 prior therapies?

On a final note, we are asking for the committee members to use your clinical and scientific expertise to assess the benefit-risk

profile of duvelisib, based on the data and discussions presented at this meeting today. Thank you. This concludes my presentation.

DR. GARCIA: Thank you, Dr. Richardson.

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

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

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

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

We will now proceed with presentations from Secura Bio, Inc.

Applicant Presentation – David Sidransky

DR. SIDRANSKY: Thank you.

I am David Sidransky, a paid clinical advisor for Secura Bio and professor of oncology at Johns Hopkins University. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policy.

Today we will discuss duvelisib, which is marketed under the trade name Copiktra, and is indicated for the treatment of adult patients with relapsed or refractory CLL or SLL, after at least 2 prior therapies. In September of 2018, duvelisib received full approval, also known as regular approval. Since it's not an accelerated approval, confirmatory evidence was not required. The

approval was based on DUO, a randomized trial of duvelisib versus ofatumumab in patients with CLL or SLL who had received at least one prior treatment.

The trial showed a statistically significant and clinically meaningful benefit in PFS, the standard endpoint for approvals of CLL drugs. The DUO trial demonstrated an acceptable and manageable safety profile with a positive benefit-risk. In order to maximize the benefit-risk ratio consistent with FDA's principle of regulatory flexibility for serious and life-threatening diseases, the FDA recommended and granted full approval for the subgroup of patients with two or more prior therapies.

There were 3 postmarketing safety requirements: the communication REMS to inform prescribers and patients; the potential risk of treatment, including serious infections and autoimmune toxicities; updated long-term safety from all the ongoing clinical trials; an updated report of OS with 5 years of follow-up; and the characterization of long-term survival for patients

treated with duvelisib. All PMRs were met in a timely manner. The totality of the evidence from DUO and the PMR demonstrate that the favorable benefit-risk profile of duvelisib has not changed since approval under its conditions of use.

I will now review the events leading up to this ODAC. Per the PMR, we submitted OS data in June of 2021. The FDA confirmed receipt and did not make any comments or requests. Specifically, no safety concerns were raised more than a year ago. In September, the FDA approved the dose increase to 40 milligrams BID in patients on moderate CYP3A4 inducers after reviewing the drug interaction study they requested we conduct. Again, no safety concerns were raised.

We subsequently submitted the same OS data to the European CHMP. They decided that the updated results reflected accrual of adverse events only for a small group of duvelisib patients, and were inconclusive. The European Agency recommended updates to the approved product characteristics information.

Approximately 6 months after submitting the updated overall survival data, the FDA asked for additional analysis for their use at the April 21 ODAC without sponsor. The ODAC recommended that for PI3K inhibitors in development, randomized-controlled trials with OS assessment should be required. Indeed, DUO was already conducted, according to these recommendations. After review of the updated OS data, the FDA requested that the sponsor issue a Dear Health Care Provider communication, informing prescribers of the results. The sponsor submitted the letter for FDA review and distributed it. The sponsor also submitted a prior approval supplement to update the label, with results communicated in the DHCP. On June 15, the FDA informed the sponsor that the NDA would be discussed at a product-specific ODAC.

We will show you today that the benefit-risk ratio for duvelisib remains positive under the conditions of its approval for the population of refractory or relapsed CLL patients who have previously received 2 prior therapies where the

unmet need remains high. Duvelisib was approved with a statistically significant and clinically meaningful benefit in PFS and overall response rate from the DUO trial. The interim and final OS data in the indicated population remains neutral.

In the indicated population, the OS rate favored duvelisib for the first 3 years, and as expected, the data after 3 years were confounded by massive unbalanced crossover to duvelisib on the control arm. Indeed, a hazard ratio of 1.06 with very wide confidence intervals does not support the conclusion of detriment in survival. Likewise, an alternative OS assessment, mean survival time was 39-and-a-half months for duvelisib versus 38.6 months for ofatumumab, and they are comparable and do not support a detriment to survival. *start

The updated safety data demonstrated no change in the safety profile since 2018. It should be noted that the accrual of safety events were heavily impacted by ascertainment bias due to the time limited at administration of ofatumumab and the lack of collection of background CLL adverse

events during follow-up on that arm. The totality of the data thus demonstrates that the benefit-risk profile of duvelisib remains positive, and that there is no new evidence to suggest that this has changed since its approval in 2018.

I would like to highlight some of the key points we will clarify in our presentation today. The FDA requires an assessment of long-term OS and informed benefit-risk. We agree that randomized OS data are important to assess safety. The FDA points out that the approved and ethical trial design led to a large imbalance in crossover. Again, we agree, and of course the consequence of the differential crossover is that we are eventually comparing duvelisib to duvelisib.

The FDA asserts that the OS hazard ratio of 1.09 in the ITT population and 1.06 in the labeled indication points to a decrement in survival. Our interpretation of these results differ. An overall survival HR near 1 was expected based on the design and the benefit of duv [ph] received by patients after crossing over from the ofa [ph] arm. Wide

confidence intervals were also expected. The appropriate interpretation of such an analysis is that there is no advantage or detriment in overall survival.

Similarly, we agree with the FDA that there's a total difference of three additional deaths in the duvelisib arm. It was expected that the null hypothesis would be reached based on the trial design, as clearly evidenced by the overlapping KM curves.

The FDA's position is that drugs are evaluated based on the trial design even if one drug is fixed before a time, based on its intended use. While we agree, it is important to remember that this is only relevant when the patients remain on the randomized treatment.

The FDA has great concerns regarding an increase in fatal infections from interim to final analysis. In fact, there's no appreciable change in the rate of fatal infections in patients treated with duvelisib, and no new signal for these events. Furthermore, per approved protocol, no safety data

was tabulated in the ofa arm after treatment, leading to an ascertainment bias which exaggerated the apparent difference between the arms.

The FDA has questioned that the optimal dose of duvelisib was adequately determined. In fact, comprehensive dose ranging was completed prior to initiation of the pivotal trial. The dose selected was one-third of the MTD, and both 15- and 25-milligram capsules are approved for flexibility. Finally, the FDA has asserted that PI3K inhibitors as a class have shown a pattern that decreased overall survival. A balanced view of the class demands consideration of the indicated patient population. Clinical trials with PI3K inhibitors in relapsed and refractory CLL patients have consistently shown a neutral or positive OS signal, supporting a positive benefit-risk of PI3K inhibitors specifically in relapsed or refractory CLL.

Following my introductions, Dr. Susan O'Brien from the University of California Irvine will discuss the disease background and unmet need;

Dr. Matthew Davids from the Dana-Farber Cancer Institute will review the efficacy and safety data; and then I will return to present the overall survival data and discuss benefit-risk. Dr. Davids will then conclude by providing his clinical perspective. In addition, we have the consultants listed on this slide available to assist in answering your questions.

I will now turn the podium over to Dr. O'Brien.

Applicant Presentation – Susan O'Brien

DR. O'BRIEN: Thank you, Dr. Sidransky.

Good morning. My name is Susan O'Brien, and I'm a professor of medicine in the Division of Hematology and Oncology at the University of California Irvine. I am a paid consultant to the sponsor, but I have no financial interest in the outcome of this meeting.

Chronic lymphocytic leukemia is the most frequent type of leukemia in Western countries. It typically occurs in elderly patients and has a highly variable clinical course. It's

characterized by the progressive accumulation of monoclonal B lymphocytes in blood, bone marrow, and lymphoid tissue. Due to the chronic nature of the disease, the prevalence of CLL in the U.S. is high. Because cure is not possible in the vast majority of patients with CLL, they will be treated with multiple agents over the course of their lifetime. As such, there continues to be an unmet medical need for safe and effective therapies.

The median age of diagnosis of CLL is 70 years, which itself presents challenges in the treatment of this disease due to comorbidities and concomitant medications. The disease is heterogeneous. Immunosuppression is inherent in the disease state, and it can lead to frequent infections. In addition, the complexities of using some agents -- in particular, venetoclax -- may lead to differences in the treatment algorithm between that seen in academic centers versus community locations.

This placebo data from the German CLL trial that randomized high-risk CLL patients to early

intervention with ibrutinib or placebo helps us understand the background complications that occur just from the presence of CLL in an elderly population. You see a high number of grade 3 or greater adverse events, and even fatal AEs on this placebo arm of the trial. Note that the majority of patients experienced an infection and that grade 3 or higher infections occurred in 14 percent of patients on no therapy. I think this paints a very vivid picture of the complexities of dealing with CLL patients and how different they are from patients with low-grade lymphomas.

Important progress has been made in the understanding of the biology of CLL with novel agents developed that target key components of the B-cell receptor pathway, namely BTK and PI3K. Another target is bcl-2, with venetoclax being the only approved bcl-2 inhibitor. Despite major advances with these novel targeted agents, CLL remains largely incurable. Currently, idelalisib and duvelisib are the only PI3K inhibitors approved for the treatment of CLL.

A unique aspect of CLL is that we only start treating patients when they become symptomatic. The considerations for first-line therapies are shown here. The selection of therapy in the relapsed setting is largely dictated by the treatment received in the first line. Therapy is employed only once patients are symptomatic.

One could reuse chemoimmunotherapy for a patient with a long PFS, but given at this point patients are older and they have more comorbidities, one would generally choose between a BTK inhibitor or venetoclax. After a BTK inhibitor discontinuation due to intolerance, one could try an alternate BTK inhibitor or change to venetoclax. For patients that progress, one would generally consider the alternate agent.

Currently available PI3Ks, including duvelisib, are an effective option for third-line-plus therapies for patients who've exhausted other options. There is not an insignificant number of patients that will reach this point in therapy, with about 13,000 estimated

in 2021.

Not all patients tolerate BTK inhibitors. Common reasons for discontinuation include cardiovascular complications, bleeding, and even sudden death. In addition, patients with known cardiovascular risk factors are not good candidates to even start BTK inhibitor therapy. Venetoclax requires intensive tumor lysis monitoring, in some cases requiring hospitalization, and it's particularly risky in elderly patients with bulky disease and renal insufficiency.

Most patients reaching third-line-plus therapy will have already seen a BTK inhibitor or a bcl-2 inhibitor, likely in combination with an anti-CD20 monoclonal antibody. For these patients, PI3K inhibitors, especially monotherapy with duvelisib, fills an important medical need.

I think the most clinically relevant difference is that duvelisib is the only PI3K approved as a single agent for relapsed/refractory CLL. Idelalisib is only approved in combination with rituximab. This is particularly important

during COVID, as we know that monoclonal antibodies significantly reduce the CLL patient's ability to respond to vaccines. In addition, most patients have almost certainly received monoclonal antibodies with prior therapy.

Importantly, the updated NCCN guidelines for CLL, which just came out in August of this year, recommend PI3K inhibitor regimens in third line for patients who are relapsed or refractory after treatment with both prior BTK inhibitors and venetoclax.

As you saw when I showed you the infection rates on the placebo arm of the CLL 12 trial on slide 4, serious infections are common in CLL patients with or without any therapy. All available therapies in the relapsed/refractory setting have shown significant rates of serious infections, and infections with duvelisib clearly fall well within this range.

Some real-world data presented at ASH in 2021 illustrates the high discontinuation rates for patients treated with either a BTK inhibitor or

venetoclax, and notably, the most common reason for discontinuation with either class of agents was toxicity. These data also show that venetoclax is being used in only 13 percent of CLL patients across all lines of therapy. Thus, these data clearly illustrate the medical need that's filled by PI3K inhibitors.

The prognosis is especially dismal for CLL patients who are resistant or refractory to both BTK inhibitors and venetoclax. In a recent retrospective study, the median overall survival in patients who progressed after both a BTK inhibitor and venetoclax was 3.6 months with a 95 percent confidence interval of 2 to 11 months.

The KM plot showed poor survival in double-resistant patients regardless of whether a BTK-i or venetoclax was used first. As more patients are now treated with venetoclax and BTK inhibitors, at some point in their treatment, the clinical problem of patients' resistant to both disease classes are already being encountered with increasing frequency.

Duvelisib received full approval in 2018 on the basis of a significant and clinically meaningful benefit in PFS in the phase 3 DUO study in comparison with ofatumumab. Full approvals for all new drugs for CLL have been on the basis of PFS because we know that PFS is associated with clinically meaningful benefit, including symptom resolution. This is particularly relevant in CLL, where asymptomatic patients are not generally treated.

This endpoint has applied to all targeted therapies, including BTK inhibitors, venetoclax, and the PI3K inhibitors. Duvelisib's approval is thus not unique in this setting. Note, the comparator arm for full approvals in CLL has most commonly been a single-agent antibody or chemoimmunotherapy.

Both idelalisib and rituximab, as well as duvelisib, have boxed warnings for immune-mediated adverse events, including fatal and/or serious infections, diarrhea or colitis, and pneumonitis. However, the label for idelalisib includes

additional boxed warnings for hepatotoxicity and intestinal perforation, and the one for duvelisib includes an additional boxed warning for cutaneous rash. Given the availability of these agents over a span of 4 to 7 years, physicians are well aware of these risks and are able to adequately manage them. Overall, there's a positive benefit-risk ratio for PI3K inhibitors in the third-line-plus CLL setting, where options are quite limited.

To summarize, CLL is generally an incurable disease, and most patients will wind up being treated with multiple agents, eventually becoming relapsed or refractory to BTK inhibitors, or venetoclax, and the anti-CD20 monoclonal antibodies. Thirteen thousand patients received third-line therapy in 2021. Younger patients, who would otherwise live a long time, will eventually become resistant to BTK inhibitors and venetoclax.

Duvelisib has been fully approved for more than four years, and is the only PI3K inhibitor option approved as monotherapy, filling an important medical need for non-overlapping

mechanisms of action in the third-line setting. The efficacy of duvelisib is uncontroversial, and no new evidence has called this into question. Duvelisib provides patients with clinically meaningful benefits and significantly prolonged remissions, and serves an important role in the armamentarium to treat CLL patients.

I will now turn it over to Dr. Davids.

Applicant Presentation – Matthew Davids

DR. DAVIDS: Thank you, Dr. O'Brien.

My name is Matthew Davids. I'm an associate professor of medicine at Harvard Medical School and director of clinical research for the Division of Lymphoma at Dana-Farber Cancer Institute. I'm a paid consultant to the sponsor, but I have no financial interest in the outcome of this meeting. I will be describing the efficacy and safety of duvelisib from the phase 3 DUO trial on which I was an investigator.

The dose rationale for DUO came from a comprehensive phase 1 dose-ranging study with an expansion cohort; 75 milligrams BID was determined

to be the MTD. The 25-milligram BID dose, a third of the MTD, was selected because it was better tolerated and similarly active.

The phase 3 DUO trial included patients with active CLL or SLL who had progressed or relapsed after one or more prior lines of therapy, were not refractory to ofatumumab, and had no prior exposure to a PI3K inhibitor or a BTK inhibitor. Patients were randomized to continuous therapy with oral duvelisib monotherapy until time of progression or unacceptable toxicity, or to a 6-month IV course of the anti-CD20 monoclonal antibody, ofatumumab.

The primary endpoint of the study was PFS by independent review in an ITT analysis set, with a variety of secondary endpoints. The primary analysis of DUO was conducted in May of 2017 with a final database lock in January of 2021. 319 patients were randomized with 160 in the duvelisib and 159 in the ofatumumab arm.

At the interim analysis, 124 patients, or 78 percent, of the duvelisib patients had discontinued therapy, and only 34 were still on

treatment. In contrast, 100 percent of the ofatumumab patients had discontinued therapy. Of these, approximately two-third of patients discontinued therapy as planned after the 6-month treatment course, and the next most common reason for discontinuation was disease progression. As discussed before, ofatumumab patients were followed for PFS and OS, but safety data were not collected following 30 days after last dose.

It is crucial to understand the final analysis of DUO included additional safety data from only the 34 duvelisib patients who had ongoing treatment at the time of approval and additional PFS and OS follow-up for both arms. Patients who remained on duvelisib at time of final analysis were given the option to participate in an extended access program.

After confirmed progression, patients were permitted to enroll in a crossover extension study, as shown in more detail on the next slide. A total of 74 patients progressed on the duvelisib arm; of those, only nine crossed over to ofatumumab, shown

here in gray on the right. In contrast, most who progressed on ofatumumab, 90 of the 101 patients, crossed over to duvelisib, shown in the dark blue. As you will hear from Dr. Sidransky, this difference in crossover has impacted the overall survival analysis.

In DUO, baseline demographics were well matched between the treatment groups, both in the ITT population shown on the left and in the labeled indication of two or more prior lines of therapy, on the right. The median age was around 68 to 70 years with a male predominance and mostly good performance status.

About 20 to 30 percent of patients had high-risk disease with deletion 17p or TP53 mutation. About half entered the study with high tumor burden, including a high absolute lymphocyte count and bulky lymph node disease. There was a median of 2 prior lines of therapy in the ITT population and 3 prior lines of therapy in the labeled indication. The study also included patients who were refractory or had early relapse

after their prior line of therapy.

Most patients had prior chemoimmunotherapy, and about 80 percent of patients had prior anti-CD20 based therapy. The primary endpoint was PFS by a blinded independent review committee. On the left, you can see in the ITT analysis that the PFS for duvelisib was superior to ofatumumab, with a hazard ratio of 0.52. In the labeled indication on the right, there was an even greater benefit for duvelisib over ofatumumab, with a hazard ratio of 0.40.

This forest plot shows that PFS consistently favored duvelisib across several different prespecified subgroups, whether by cytogenetics or other clinical characteristics. Overall response rate was significantly higher in the ITT and labeled indication on the duvelisib arm, 78 percent shown in blue, compared to the ofatumumab arm, 38 percent in gray. In this subgroup analysis of overall response, we again see that, as with PFS, all the different prespecified subgroups favored duvelisib, including cytogenetics or clinical

characteristics.

In the crossover study, specifically in the 90 patients who were treated with duvelisib after crossing over from ofatumumab, the overall response rate was 77 percent, and this rate was equivalent in patients with high-risk deletion 17p or mutant TP53 and, importantly, in patients who were refractory to prior ofatumumab during the parent study.

Median PFS for patients who crossed over from ofatumumab to duvelisib was about 15 months in all patients who crossed over, in blue, as well as in those at high risk, in green. Recall that the PFS in the ofatumumab arm was 9.4 months in the parent study. These data show that even after failing prior ofatumumab therapy, duvelisib provided clinically meaningful efficacy benefits.

Now let's discuss the safety analyses from the DUO study. Safety data were collected during the time on treatment and for 30 days post-final dose. This means that for the ofatumumab arm, there was no safety data collection after a maximum

of 6 months plus 30 days. After this point, additional CLL-related AEs are only accumulating in the patients on duvelisib treatment and are not being recorded in the ofatumumab arm. Recall from Dr. O'Brien's presentation that patients with CLL have a high rate of background AEs, even in the absence of treatment.

During the 24-week period after the first dose, shown on the left, when both groups were still being monitored for toxicities, there were numerically higher rates of toxicities in duvelisib compared to ofatumumab, however, notably the rate of fatal AEs was equivalent. In the overall study period, on the right, the duvelisib arm had higher rates of treatment-emergent AEs, serious AEs, discontinuations, dose holds, and fatal AEs, as would be expected with longer follow-up and recording of events only on the duvelisib arm.

When looking specifically at the first 24 weeks, higher rates of diarrhea and slightly higher rates of neutropenia and pyrexia were observed with duvelisib compared to ofatumumab. As

I'll show you, these differences are less than when we look across the entire study period.

Most common toxicities for duvelisib are represented here, all grades on the left and grade 3 or higher on the right. There were slightly higher rates of hematologic toxicities with duvelisib compared to ofatumumab, but overall, these rates were similar. The most significant differences were in diarrhea, pyrexia, nausea, and pneumonia, which were higher with duvelisib compared to ofatumumab. Note that these are the known AEs of duvelisib at the time of approval, which are reflected in the current USPI.

Diarrhea, neutropenia, colitis, and pneumonia were the most common AEs leading to dose hold or dose reduction in the duvelisib arm, and note that there are many more dose holds than dose reductions. Similarly, diarrhea, colitis, and pneumonia were the most common AEs leading to treatment discontinuation in the duvelisib arm, and again, these are the known AEs, which are reflected in the current USPI for duvelisib.

As mentioned before, the final analysis included additional follow-up data only from 34 patients, those who had undergone treatment at duvelisib at the time of the primary analysis. As you can see, even with a maximum duration of exposure to duvelisib of 311 weeks, or nearly 6 years, there was minimal change in the rates of AEs, indicating clearly that there were no new safety concerns. Note that these are the known AEs of duvelisib at the time of approval, which are reflected in the current USPI and do not represent new evidence pointing to additional toxicity.

In summary, duvelisib monotherapy resulted in a statistically significant and clinically meaningful improvement in PFS and ORR compared to ofatumumab in patients with relapsed or refractory CLL or SLL , including those with high-risk disease. This treatment effect was consistent across all prespecified subgroups.

A high proportion of patients responded to duvelisib treatment after crossover, and the safety profile of duvelisib is well characterized,

manageable, and reflected in the prescribing information. Importantly, there is no new safety evidence to support a change in the favorable benefit-risk profile since approval. Thank you, and I'll now turn the presentation back to Dr. Sidransky.

Applicant Presentation – David Sidransky

DR. SIDRANSKY: Thank you, Dr. Davids.

Overall survival in both the interim and final analysis is an exploratory secondary endpoint with no alpha allocation. First, the results must be interpreted with caution because of the extensive crossover to duvelisib. Almost all patients that were randomized to ofatumumab crossed over within 24 months of treatment to duvelisib.

Second, almost all patients were off study drug after 2020, making attribution of causality to randomized therapy through the 2021 database lock tenuous. The therapy they received after study drug was completely at random.

Third, the analysis will never be fully mature given the difficulty in maintaining

long-term follow-up on patients once they stop study drug. It is therefore not surprising that the OS results are essentially neutral, the null hypothesis at both the interim and final analyses.

Here again are the interim results at time of full approval. In the ITT analysis, the KM curves were overlapping, except at the very end where patients were long off the study drug. In the labeled indication, the curves began to separate within the first year and did not cross at the end. The hazard ratio was 0.82 for the labeled indication versus 0.99 for ITT, and the lower HR for OS in the indicated subgroup is directly consistent with the lower HR for PFS at that time.

Now let's look at the final analysis for the ITT population 2 and a half years after the drug was approved. Data lock occurred in January of 2021. The curves remain very similar, and they're again overlapping, except at the very end where most patients were long off study drug. HR remains neutral at 1.09 with wide confidence intervals. The difference in the mean survival time is

12 days, however the extensive crossover impacts the ability to interpret the results, as you will see.

The figure is the reminder regarding a large and unbalanced crossover to duvelisib. The comparator arms in the analysis are representative by the two brackets essentially showing that we are comparing duvelisib with duvelisib post-ofatumumab. The much larger median duration of treatment on duvelisib impacted the accrual of AEs, as you heard from Dr. Davids' presentation, and it's also impacted the overall survival assessment, as you will see in the next slide.

The swimmer's plot illustrates the extensive crossover, with the end of the line representing death, the dots, or censoring. The blue lines represent treatment with duv [ph] and time of follow-up, and the red lines show treatment with ofa and the time of follow-up after last dose. The change in color indicates the time of crossover.

Look how similar these plots are overall for both arms. The figure on the left shows relatively

few patients crossed over to ofa with little overall exposure to ofatumumab. In contrast, the figure on the right shows the very large proportion of patients that crossed over to duv and the appreciable amount of time they remained on it, all blue. This extensive exposure to duv in the ofa arm limited the ability of the trial to demonstrate any difference in overall survival, and that does not support the conclusion that duvelisib has a detrimental impact on OS.

Now let's take a look at a comparison of the interim analysis, at left, and the final analysis on the right for the labeled indication. In the final analysis, the KM curves cross after about 4 years, when essentially all patients be left on study in both arms are on duv. We know the patients that crossed over benefited from the prolonged PFS while on duvelisib. After failing duvelisib in the last year, patients were treated by physicians' choice of dozens of different regimens, further complicated by very few patients at risk and very few events in the tails of the

curves.

In summary, the final analysis of hazard ratios is inconclusive. The wide confidence interval indicates the lack of precision. The shift in the hazard ratios from the interim to final analysis likely reflects the instability of the estimate. In contrast, the mean survival time was generally stable between the interim and final analysis, with relatively small confidence intervals.

The differences in mean survival times are one month or less in both the ITT and the indicated population. Taken together, the mean survival times support the conclusion that duvelisib has a neutral impact on overall survival. The mean survival time may be more clinically meaningful and interpretable than the point estimate for the hazard ratio in this trial, especially in the indicated population where there was a crossing of the KM curves.

By the way, the criticism in FDA's briefing document regarding MST, or the mean survival time,

applied equally to the hazard ratio assessment, and that both have no alpha allocations and are dependent on truncation time, which is negligible here. Finally, as Dr. Davids showed you, patients who progressed on the ofa arm benefited from treatment with duv, limiting the ability to show a difference between the treatment arm.

At the final analysis, there were 10 more deaths in the duv arm compared with the ofa arm in the overall study population. In the labeled indication there was an imbalance of 3 deaths. Note that this imbalance is further explained by the depletion of susceptibles, as will be [inaudible – audio lost].

DR. GARCIA: Dr. Sidransky, I think you went off.

(Pause.)

DR. GARCIA: Dr. Chen, do we know if he got disconnected?

DR. S. CHEN: Hi, Dr. Garcia. Just a moment; we're checking. We'll let you know momentarily. Thank you.

DR. GARCIA: Thank you.

(Pause.)

DR. GARCIA: Dr. Sidransky, are you able to reconnect?

(No response.)

DR. O'BRIEN: This is Dr. O'Brien. If we don't have Dr. Sidransky able to connect, I could continue the presentation for him, if that would be useful.

DR. GARCIA: I don't see why not, Dr. O'Brien. If you feel comfortable presenting that section of survival and benefit-risk, I would be ok with that.

DR. O'BRIEN: Okay. And then if Dr. Sidransky gets back on, I can hand it back over to him.

DR. GARCIA: It should be fine.

Dr. Chen, is that acceptable for us to move forward that way?

DR. S. CHEN: Sounds good. Thank you.

DR. GARCIA: Alright. Perfect.

Susan, go ahead.

DR. O'BRIEN: Okay. If you don't mind, I'll start on this slide -- I'll start over again because I'm not sure where he dropped off.

So a higher number of deaths before progression were observed at the interim and final analysis in patients treated with duvelisib. Because disease progression occurred more often and more quickly on the ofatumumab arm, the number of patients on the ofatumumab arm who were susceptible to an event of death before progression rapidly became very small. This makes this analysis subject to the well-known depletion of susceptible bias.

Note that at the interim analysis, there were 12 deaths before progression on the ofa arm, and at the final analysis, there are still 12 deaths before progression on the ofa arm. This is because very few patients remain progression-free on the ofa arm.

When interpreting these data, the depletion of susceptibles bias creates the illusion of a protective effect of ofa in preventing death before

progression, when we are actually observing a lack of efficacy of ofatumumab in preventing progression. In contrast, the increased number of deaths before progression on the duva [ph] arm is related to the fact that patients treated with duvelisib were on drug for much longer without progression.

DR. SIDRANSKY: Thank you, Dr. O'Brien. I can take it from here.

DR. O'BRIEN: Okay. Great.

DR. SIDRANSKY: The refractory subgroup was prespecified in the protocol and defined as patients who progressed within 12 months on chemotherapy. The KM curves in this subgroup began to separate around one year, and the hazard ratio was 0.77. The difference in mean survival time favored duvelisib by 6.2 months. While exploratory, these results support the hypothesis that in heavily pretreated or refractory disease, duvelisib has a positive rather than detrimental impact on survival.

The first two rows of the forest plot

demonstrate the FDA concerns related to the PI3K inhibitors in treatment-naive or mixed populations with hazard ratios to the right of 1. However, when comparing HRs across studies, it is important to consider both the disease and the patient population. When we conduct a fair comparison across phase 3 trials with PI3K inhibitors, specifically in relapse and refractory CLL patients, we see a trend towards favorable outcome.

Within the DUO trial, a trend in HR closer to UNITY is observed in the ITT and the labeled indication of patients who have received more than 2 prior lines of therapy. The refractory subpopulations of DUO, which is similar to patients included in the 116 and 119 studies of idelalisib and rituximab, show comparable OS HRs. These data support the positive benefit-risk profile of PI3K inhibitors as the class in patients with refractory and relapsed CLL, and support a continued favorable benefit-risk profile of duvelisib monotherapy under conditions of use in the labeled indication.

The evidence presented to date does not

support a conclusion that duvelisib has a detrimental impact on overall survival. In the indicated population, the hazard ratio for OS was 1.06 with a wide confidence interval and nearly identical to the OS rates at 3 years. The mean survival times are also comparable.

The KM curves are essentially superimposable and do not cross until after 45 months, which is well after most patients have discontinued treatment with either study medication. The analysis of OS is confounded by crossover and, as expected, overall suggests a neutral effect on survival.

Regarding risk management, the safety profile presented today is already included in the approved product label and boxed warning. The company continues to market the drug exclusively for patients with 2 prior lines of therapy. The communication REMS surveys demonstrate that physicians understand both the conditions of use and the risk of treatment. Ongoing pharmacovigilance activities do not indicate a

change in the risk profile since approval. And lastly, the company has submitted a prior approval supplement to include the updated OS data in the product label.

In conclusion, the totality of evidence demonstrates the safety profile of duvelisib is consistent with the safety at time of approval. In this regard, I would like to address the four key points in the FDA's introductory remarks. First, that fatal and serious toxicities observed at time of approval did not result in the decrement in OS over time. At interim, there was no suggestion of a harm in OS in the labeled indication, and at final analysis there was no detriment in OS. There was also no meaningful change in the profile of fatal toxicities over time.

Second, the increase differences in death due to AEs, including fatal infections, was expected as there were no remaining patients on ofatumumab treatment, and therefore additional deaths due to treatment-emergent AEs could not be accrued on the ofatumumab arm.

Third, the difference in death before progression, 31 versus 12, is expected and can be explained by significantly increased time on duvelisib without progression, and the number of deaths due to progression in the ofa arm, 12, remains unchanged from interim to final analysis, or the control arm consistent with the expected depletion of susceptible. Fatal adverse events post-crossover are expected and consistent with the current product label and background rates in elderly at-risk CLL patients.

With regards to benefit, there are statistically significant and clinically meaningful PFS benefits in the primary and the final analysis. The QoL data points to benefit and quality of life. There is no new evidence to support a change in benefit-risk for duvelisib since approval. The totality of data demonstrates a favorable benefit-to-risk profile for duvelisib, which is also consistent with that of another PI3K inhibitor approved in refractory and relapsed CLL, idelalisib, which remains on the market, indicating

that this benefit-risk profile is acceptable for patients with relapse and refractory CLL.

To our knowledge, the agency has not issued public safety alerts or taken other actions against the only other two approved agents in the class at this time. There is therefore no new evidence that demonstrates that the drug is not safe or effective under conditions of use. As you will hear further from Dr. Matt Davids, duvelisib remains an important treatment option for patients with relapsed and refractory CLL.

Dr. Davids?

(No response.)

DR. GARCIA: Dr. Davids, we cannot hear you. I don't know if you're in mute.

(No response.)

DR. DAVIDS: Sorry. Can you hear me now?

DR. GARCIA: Yes. Please go ahead.

Applicant Presentation – Matthew Davids

DR. DAVIDS: Thank you, Dr. Sidransky.

I'm happy to conclude with my clinical perspective. As you will hear, duvelisib is an

important treatment option for patients with relapsed or refractory CLL. This is a view that's shared by my CLL colleagues, as well as the largest CLL patient organization and the over 200 patients who submitted their comments for this meeting.

The DUO study demonstrates that duvelisib provides a clear PFS advantage over ofatumumab in patients with two or more prior lines of therapy. While there are well-recognized immune-mediated and infectious adverse events with duvelisib, our experience shows that these AEs are usually manageable through dose holds, reductions, and supportive care. As you heard, there is no difference in overall survival with longer term follow-up, as was expected with the crossover design of this study.

DUO had the same comparator arm in a similar design to RESONATE, the registrational trial for ibrutinib, which is the most commonly used drug for CLL. Overall, the DUO study demonstrates a positive benefit-risk balance.

So where do we use PI3K inhibitors like

duvelisib? The majority of CLL patients are treated with frontline BTK inhibitors, but eventually patients will either progress or become intolerant. Venetoclax based therapy is often used next. When they progress on venetoclax, PI3-kinase inhibitors like duvelisib become the best option. The small number of patients who begin with venetoclax eventually will progress and go on a BTK inhibitor in the second line. When they progress, PI3-kinase inhibitors like duvelisib are used. Duvelisib is also used when patients have intolerance to BTK inhibitors.

A minority of CLL patients are still getting frontline chemoimmunotherapy, and when these patients progress, they typically get venetoclax-based treatment, followed by a BTK inhibitor or vice versa. In subsequent lines, PI3-kinase inhibitors like duvelisib are the best option.

Despite the approval of many CLL agents, relapse and refractory patients often run out of safe and effective choices. The list noted in the

FDA briefing document includes drugs that are either historical and not used in practice or agents used in earlier lines of treatment, and resistance can ensue when reused in later lines, or also includes agents that are not approved in CLL. In contrast, duvelisib is the only monotherapy approved specifically in third-line CLL, and as recently as last month, it continues to be recommended in third line in the updated NCCN guidelines.

Turning now to the benefits of duvelisib, PFS is a particularly meaningful endpoint in CLL. Life-threatening infections are a hallmark of the disease and are commonly either a precursor to or a consequence of progression. Prolonging PFS often means delaying significant complications of the disease. In patients with two or more prior therapies, the PFS benefit for duvelisib was associated with a quality-of-life benefit, and importantly, prolonging PFS allows patients to bridge to novel and investigational agents.

Lastly, CLL patients are not necessarily

treated at the time of progression. At time of crossover, patients are already symptomatic, yet despite the differential crossover, PFS at final analysis remains markedly favorable for duvelisib.

I'd like to illustrate this concept with a couple of representative patient cases. The first is a 57 year-old firefighter with high-risk disease. After a year of observation, he received ibrutinib with a good response but progressed after about 6 years. He was switched to venetoclax and had a good response, but progressed again after about 2 years. He then received duvelisib and achieved a good quality partial remission. This served as a bridge to allogeneic transplantation about 9 months later, and he's now in complete remission over 3 years out from transplant.

This 75-year-old patient had a similar course, first with ibrutinib and then venetoclax, and had a good response to each, but progressed after 5 years. She was not a good candidate for aggressive approaches like allogeneic transplantation, so she was started on duvelisib

and had a good partial remission. This allowed her to attend her granddaughter's wedding. Now, after about one year, her CLL has begun to progress again on duvelisib, but she's optimistic about new investigational therapies on the horizon.

Now I'd like to discuss a letter regarding PI3-kinase inhibitors that the FDA submitted to Lancet Oncology, and it was published this summer. They noted that some randomized studies of PI3-kinase inhibitors had overall survival hazard ratios that were numerically in favor of control arms. It's important to recognize that none of those results were statistically significant. Several of my colleagues and I submitted a response to this letter. In it, we highlighted the transformative and life-saving results we've observed with these drugs over the last decade, and that there is no difference in overall survival across these studies.

The largest CLL patient organization, CLL Society, submitted the letter to the FDA in which they recognized the important role of PI3K-kinase

inhibitors, particularly in high-risk patients who have progressed on BTK inhibitors and venetoclax. There were 40 signatories of this letter, representing the consensus of many of America's leading investigators in CLL.

To conclude, the DUO trial confirmed a significant and clinically meaningful PFS advantage, with a manageable safety profile and no significant difference in overall survival, now with longer term follow-up. Many patients in our practices benefit from duvelisib, which is typically used as third-line therapy and may serve as a bridge to other therapies.

The CLL investigator and patient communities are united in support of this important option for relapsed CLL patients. The risk-benefit profile of duvelisib is favorable, and there is no evidence of change in the benefit-risk since approval. This concludes our presentation. Thank you for your time and consideration.

DR. GARCIA: Thank you, Dr. Davids.

We will now proceed with the FDA

presentation from Dr. Deepti Telaraja.

Dr. Telaraja?

FDA Presentation – Deepti Telaraja

DR. TELARAJA: Hi. Good morning. I'm Deepti Telaraja, a pediatric hematologist/oncologist in the Division of Hematologic Malignancies II, at the FDA. I will be presenting the FDA's discussion on the updated benefit-risk assessment of duvelisib in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma. The members of the FDA review team are listed here. My presentation represents their collective input.

I would like to begin with a brief overview of the PI3K inhibitor class. Overactivation of the PI3K pathway is common in hematologic malignancies and results in dysregulated cell growth and survival. PI3K inhibitors are targeted immunomodulatory drugs, which inhibit different isoforms of PI3K. Based on the mechanism of action and the drug's effect on lymphocyte subsets, particularly T regulatory lymphocytes, the toxicity

profile is distinct.

The toxicities seen include infections and immune-mediated toxicities such as diarrhea or colitis, hepatotoxicity, pneumonitis, and rash. As shown in this schematic here, duvelisib is a dual delta and gamma PI3K inhibitor. The PI3K inhibitors that have received approval and the isoforms that they inhibit are also shown here.

The FDA discussion for today's ODAC will focus on the issues with duvelisib following a 5-year overall survival analysis from the randomized DUO trial in patients with CLL and SLL. The central issues under discussion are the potential detriment in overall survival in patients treated with duvelisib, the toxicity and tolerability concerns, and concerns regarding the selected duvelisib dose of 25 milligrams.

This will be followed by an overview of the safety concerns with the PI3K inhibitor drug class, with potential detriments in overall survival seen across multiple randomized trials and the notable toxicity profile seen across the class. These

issues will conclude in a current benefit-risk evaluation of duvelisib for patients with relapsed or refractory CLL or SLL.

In September 2018, duvelisib was approved for patients with CLL or SLL, and follicular lymphoma at a dose of 25 milligrams BID. The FL indication was an accelerated approval based on a single-arm trial, however, due to inability for the sponsor to provide evidence for verification of clinical benefit, the FL indication was voluntarily withdrawn from the U.S. market in December 2021. The focus of the discussion today will be related to the indication in patients with CLL or SLL.

The approval of duvelisib for CLL or SLL was based on the DUO trial. This was an open-label trial that randomized patients with relapsed or refractory CLL or SLL after at least one prior line of therapy between duvelisib or ofatumumab, an anti-CD20 monoclonal antibody. The primary endpoint was progression-free survival per independent review committee, and key secondary endpoints were overall response rate and overall

survival. Of note, following IRC confirmed disease progression, crossover to the alternate treatment arm was allowed.

This table shows the efficacy data supporting the initial approval of duvelisib. In patients with two or more lines of therapy, a 7-month improvement in median PFS was demonstrated on the duvelisib arm, with a hazard ratio of 0.4. There was also an improvement in overall response rate with an ORR of 78 percent on the duvelisib arm and 39 percent on the ofatumumab arm. At the time of initial approval, overall survival was immature, with a median of 24 months of follow-up. Median OS was not reached in either arm and the estimated hazard ratio was 0.82.

Due to significant toxicity and tolerability concerns, which I'll cover later in this presentation, several mitigation measures were implemented to manage the risks of treatment with duvelisib. These included a communication REMS and a boxed warning to address the risks of fatal and/or serious infections, diarrhea or colitis,

cutaneous reactions, and pneumonitis.

Due to the significant toxicity concerns and the immaturity of the overall survival data with the need for longer follow-up, two postmarketing requirements for safety were issued. The first was to characterize the safety of long-term treatment with duvelisib at a dose of 25 milligram BID across multiple studies, including the DUO trial. The second was to submit overall survival data from the DUO trial with 5 years of follow-up.

The first issue I'll discuss is the potential OS detriment seen in the duvelisib arm compared to the ofatumumab arm, based on the updated 5-year overall survival analysis. This potential detriment was seen both in the ITT population and the indicated population, those with two or more prior therapies.

This slide shows the updated overall survival data with 5 years of follow-up in the ITT population. There was a higher number of deaths observed on the duvelisib arm, with 80 deaths on the duvelisib arm versus 70 deaths on the

ofatumumab arm. There was an 11-month detriment in median overall survival, with an estimated hazard ratio of 1.09.

This slide shows the updated overall survival data with 5 years of follow-up in the indicated population, those with two or more prior therapies. Again, there were more deaths on the duvelisib arm; 53 versus 49 on the ofatumumab arm, with an estimated hazard ratio of 1.06. In the setting of a benefit in PFS and overall response rate, the potential detriment in overall survival in both the ITT and indicated populations indicates a primary safety concern with duvelisib and the potential for harm.

In both populations, there was a higher rate of death due to adverse events on the duvelisib arm. Fatal toxicities contributed to 14 percent of deaths on the duvelisib arm compared to 3 to 4 percent on the ofatumumab arm, as shown in the table here.

This table shows the FDA adjudicated deaths due to adverse events in the safety population,

which is defined as deaths occurring within 30 days of the last dose of treatment or deaths with a causal relationship to study treatment. Infection was the greatest driver of deaths due to adverse events on the duvelisib arm, causing 9 percent of deaths as compared to less than 1 percent on the ofatumumab arm. The specific types of infections resulting in deaths on the duvelisib arm were primarily sepsis and pneumonia. The next most common category of deaths on the duvelisib arm was respiratory, which included deaths related to the known risk of pneumonitis and cases of respiratory failure with related infectious complications.

As mentioned previously crossover upon disease progression was permitted on the DUO trial. Fifty-seven percent of patients on the ofatumumab arm crossed over to receive duvelisib and 6 percent of patients on the duvelisib crossed over to receive ofatumumab. Because of the substantial crossover in the DUO trial, I'd like to take a moment to address the interpretation of overall survival data in the presence of crossover.

We acknowledge that crossover can impact the assessment of time to event endpoints, such as overall survival. Specifically, in the case of a drug with substantial and fatal toxicity such as duvelisib, crossover from the control arm to the investigational arm may result in harm to the control group. If the crossover results in additional overall survival events in the control group due to toxicity, this can actually mask a difference that would have favored the control arm in the absence of crossover. So for the DUO trial, where substantial crossover to the duvelisib arm occurred, the finding of a potential overall survival detriment with duvelisib, in spite of substantial crossover, is especially notable.

In order to characterize the impact of crossover in the DUO trial, we further analyzed patient-level data and performed additional statistical analyses. The data are consistent with the potential for harm and a potential detriment in overall survival.

In order to characterize the outcomes of

patients who crossed over to the alternate treatment arm, we assessed the number of deaths due to adverse events on each arm following crossover. In those who crossed over from duvelisib to ofatumumab, there were no deaths due to adverse events. In those who crossed over from ofatumumab to duvelisib, 10 percent of patients died due to adverse events. Again, the primary causes were fatal infections, including sepsis and pneumonia. The data shown here reinforces the concern for toxicity in patients treated with duvelisib.

In order to account for the effects of crossover on the OS results, the FDA performed sensitivity analyses using two different causal inference models. The results of both analyses, as shown in the table here, are consistent with the primary analysis of overall survival in the ITT population. Taken together, the primary analysis and the two sensitivity analyses demonstrate a consistent potential detriment in overall survival and support the potential for harm with duvelisib.

A consistent pattern for a potential

detriment in overall survival was also seen when evaluating the updated OS data in the prespecified subgroups. As shown in the forest plot here, the results in the majority of subgroups are consistent with those in the ITT population, again supporting the potential for harm.

It is worthwhile to note that in patients who were refractory to or had early relapse following purine analog-based treatment, a hazard ratio of 0.78 with a 95 percent confidence interval crossing 1 was seen. While subgroup analyses can be used to assess consistency of the treatment effect, they cannot be used to conclude a treatment benefit in a subgroup when the overall results are negative. Any findings of a potentially favorable effect in a subgroup would be considered exploratory, and the population of interest would require further study in a prospective trial.

Over the next few slides, I will present data related to the next two key issues, the toxicity concerns that could have potentially contributed to the overall survival results and

concerns with the selected dose of duvelisib. First, I'd like to note that the DUO trial was designed to evaluate fixed-duration therapy with ofatumumab versus continuous administration with duvelisib. Ofatumumab was given and completed by 6 months per the approved labeling, and duvelisib was administered continuously until disease progression or unacceptable toxicity.

The median exposure duration for patients on the duvelisib arm was 12 months compared to 5 months on the ofatumumab arm. Despite the variability in treatment duration, the results of this study represent the respective treatment regimens as they're intended to be administered. The results adequately qualify the risk of the treatment, particularly given that continuous treatment with duvelisib has a direct impact on the continued risk for toxicity.

This graph shows the safety results from the DUO trial, with the duvelisib arm represented in blue and the ofatumumab arm represented in green. Here, you can see that the rates of grade 3 or

greater toxicities, serious adverse events, and treatment modifications due to adverse events are all notably higher in the duvelisib arm.

The safety results from the DUO trial demonstrate that the PI3K-associated toxicities of an infection, neutropenia, diarrhea or colitis, increased AST or ALT, rash, and pneumonitis are driving the differences in safety between the treatment arms. As shown here, the incidence of pneumonitis or grade 3 or greater PI3K-associated toxicities, except for neutropenia, are 2 to 3 times or more higher in the duvelisib arm compared to the control arm.

In general, the evaluation of tolerability of a drug can also be informed through collection of patient-reported outcomes or PROs. The FDA encourages sponsors to collect PROs through well-defined PRO measures that inform how patients are feeling and functioning. Well-defined PRO measures can inform dose selection, tolerability, and interpretation of safety information.

Unfortunately, in the DUO trial, the two

selected PRO measures and endpoints were not sufficient to detect meaningful differences between arms. The EQ-5D does not adequately capture important and relevant symptoms in the patient population, and the FACIT-F did not show improvement with duvelisib as compared to ofatumumab. Given the substantial tolerability issues, which I'll cover in the next slide, a more comprehensive approach to patient-reported symptoms may have been informative regarding the tolerability and dosing of duvelisib.

This table demonstrates the higher rates of treatment modification, including dose interruption, reduction, and discontinuation due to adverse events that occurred with duvelisib as compared to ofatumumab. It is worthwhile to note that 44 percent, nearly half, of patients on the duvelisib arm discontinued treatment because of toxicity. This raises concerns about the tolerability of duvelisib and, along with the updated overall survival information, warrants an updated evaluation of the selected dose of

25 milligrams.

The 25-milligram BID dose of duvelisib was primarily selected based on data from a dose escalation and expansion study that was designed to establish the maximum tolerated dose. Doses ranging from 8 to 100 milligrams were studied, and 75 milligrams was identified as the MTD. Although activity was observed at the 15-milligram dose level, expansion was only conducted at the 25- and 75-milligram dose level.

Data from the expansion cohorts indicated that overall response rate was comparable between the 25-milligram and 75-milligram BID doses, suggesting a saturation of effect at the 25-milligram BID dose or below. 25-milligram BID was selected as the recommended phase 2 dose.

This table shows the summary of best overall response by dose level in the dose-finding study. Although the number of patients enrolled in some cohorts was quite limited, activity was observed at dose levels lower than 25-milligram BID, suggesting that lower doses may be efficacious.

The pharmacokinetic and pharmacodynamic analysis of biomarker data also support the findings of activity at lower doses of duvelisib. The figures on the left show the inhibition of phospho-AKT in tumor cells following a single dose in patients with CLL or SLL. The 25- and 75-milligram doses both achieved near maximal suppression at 1 hour and 24 hours post-dose. Unfortunately, no other doses were tested.

The figure on the right shows an overlay of the EC50 value for phospho-AKT inhibition and the steady-state PK profiles of duvelisib at different dose levels. Duvelisib concentrations at the 15-milligram dose level may be maintained above the EC50 throughout the dosing interval. Taken together, these analyses also suggest that lower doses may be efficacious.

For safety, there are exposure-response relationships observed with duvelisib, with higher exposure leading to higher rates of infection, pneumonia, and transaminase elevation. These were some of the most common toxicities leading to

treatment modification. The exposure-response for grade 3 and greater infection is shown on the slide here. With regards to efficacy in the DUO trial, no positive exposure-response relationship was observed for any efficacy endpoints, including overall response rate, PFS, or overall survival.

Taken together, there are significant safety concerns regarding the selected dose of 25 milligrams, as indicated by the high rates of adverse events and dose modification observed in the DUO trial. In addition, the lack of exposure-response relationships for efficacy, the positive exposure-response relationships for safety, and the demonstrated clinical activity at doses lower than 25-milligram BID all suggest that lower doses may be efficacious with better tolerability. These lower dose levels have not been adequately evaluated and would require further exploration to define an optimized dose.

In summary, there are three major areas of concern with the data with duvelisib from the DUO trial: overall survival, increased toxicity, and

inadequate dose optimization. With respect to overall survival, the DUO trial demonstrated a higher rate of death and death due to adverse events on the duvelisib arm. The potential detriment in overall survival occurred in the setting of a benefit in PFS and overall response rate with duvelisib, indicating a primary safety concern.

With respect to increased toxicity, the duvelisib arm demonstrated a higher rate of grade 3 or greater adverse events, serious adverse events, and treatment modifications, all of which were driven by infections and immune-mediated toxicities. And finally, with respect to dosing, the increased toxicity with duvelisib is correlated with several exposure-response relationships for safety and a lack of clear exposure-response relationships for efficacy. There was also limited dose exploration and dose optimization, which calls into question the acceptability of the selected dose in light of the updated OS data.

Next, I will present the relevant data and

discussions from the recent PI3K inhibitor ODAC. There are parallels between the overall survival and toxicity concerns with duvelisib and the concerns with the other drugs in the PI3K inhibitor class that have implications for the benefit-risk evaluation of duvelisib.

The key issues discussed at the PI3K inhibitor ODAC were concerning trends in OS across randomized-controlled trials of multiple PI3K-inhibitors, the high rates of toxicity seen across the class, and concerns about inadequate dose optimization. Additionally, the limitations of the ability for single-arm trials to support an assessment of benefit-risk for PI3K inhibitors were also discussed.

Shown here are the data that were presented at the PI3K inhibitor ODAC from 6 randomized-controlled trials, evaluating a PI3K inhibitor as monotherapy or in combination in patients with CLL or non-Hodgkin lymphoma. In these trials, potential detriments in overall survival were seen in the PI3K inhibitor arm compared to the control

arm. This pattern was even noted in the CHRONOS-3 trial, which has an estimated hazard ratio of 0.87.

In the CHRONOS-3 trial, there was decreased overall survival in the first 2 years in the copanlisib arm, followed by a crossing of the Kaplan-Meier curves. This was coupled with a higher rate of fatal adverse events in the copanlisib arm, indicating a potential risk for early mortality.

While this overall survival information is early and represents a low number of events in some trials, we are observing the same pattern across multiple trials, where a favorable impact on efficacy endpoints such as PFS or overall response rate is then followed by a potential overall survival detriment. This indicates that the overall survival concerns are a primary safety concern and is supported by the higher rates of death due to adverse events and higher rates of toxicity seen in the PI3K inhibitor arm across trials. Notably, this finding across multiple randomized trials of one class of drug is

unprecedented in oncology.

Surrounding the PI3K inhibitor ODAC, actions were taken with multiple PI3K inhibitors: duvelisib, idelalisib, umbralisib, and copanlisib. These included voluntary withdrawal of existing approval and voluntary withdrawal of new drug applications or supplemental new drug applications.

The PI3K inhibitor class has demonstrated substantial toxicity that can be fatal or serious and are related to the mechanism of action of these agents. This table shows the incidence of the PI3K-associated toxicities for the drugs in this class that have been approved for hematologic malignancies when administered as monotherapy. There's a high incidence of the respective grade 3 or greater toxicities across the class, and as you can see here, many are especially notable with duvelisib. These significant toxicity findings reiterate the safety concerns with this drug class.

Dose modification data from these PI3K inhibitors also suggests consistent tolerability concerns across the class. Again, the tolerability

profile of duvelisib is especially notable. Because of toxicity, a substantial number of patients discontinued treatment or required dose reduction or interruption.

The discussion at the PI3K inhibitor ODAC was robust and very insightful regarding this class of products. The committee all agreed that the data with the PI3K inhibitor class was concerning. The main reasons cited were the lack of adequate dose finding, the notable toxicity profile and tolerability concerns, chronic administration of these agents, and the concerning pattern of PFS benefits that were later followed by OS detriment.

The committee agreed that OS is the paramount endpoint and that it informs benefit-risk, especially in the setting of substantial toxicity. Most importantly, the committee reiterated how crucial a benefit-risk assessment is and the need for adequate data to ensure that the drug is safe and effective, and to rule out potential for harm so that we may effectively care for patients with cancer.

Now I'll turn to a current benefit-risk evaluation for duvelisib. The reason we are here today is to discuss the current benefit-risk profile of duvelisib for patients with relapsed or refractory CLL or SLL after at least 2 prior lines of therapy. First, it is important to note that the assessment of benefit-risk is continuously assessed as new information becomes available. The 5-year overall survival data from the DUO trial has prompted this updated assessment.

I would also like to highlight some key considerations about overall survival as an endpoint. Overall survival is considered the most reliable cancer endpoint. It is an objective measure of clinical benefit and is considered both a safety and an efficacy endpoint. An evaluation of toxicity is embedded in the assessment of overall survival, including the ability to assess short- and long-term toxicity.

Further, the same degree of statistical considerations that apply when overall survival is used as a primary efficacy endpoint do not apply

when overall survival is used as a safety endpoint. And lastly, the FDA requires overall survival information in any trial that uses a primary PFS endpoint in order to inform benefit-risk.

The importance of overall survival from the DUO trial is further highlighted because the 5-year overall survival analysis was issued as a postmarketing requirement. As previously mentioned, the reason for issuing this PMR was due to the concerns regarding fatal and serious toxicity and due to immature overall survival data at the time of initial approval.

Because of the importance of overall survival outcomes to patients, following the PI3K inhibitor ODAC and FDA's assessment of the updated 5-year OS data with duvelisib, an FDA safety alert was issued on June 30th. This was intended to alert patients and healthcare providers of the potential risk associated with the use of duvelisib so that they could weigh the benefit and risk of continuing duvelisib under the approved indication and make an informed treatment decision. The alert

also noted that the information with duvelisib would be discussed in a future public meeting.

As discussed throughout the presentation, the primary issues to be considered in a current assessment of benefit-risk for duvelisib include the following: a potential detriment in overall survival in the setting of a benefit in PFS and overall response rate, indicating a safety concern; a higher rate of death due to adverse events with duvelisib; fatal adverse events in patients who crossed over from ofatumumab to receive subsequent treatment with duvelisib; OS sensitivity analyses supportive of the primary overall survival results, indicating the potential for harm; substantial toxicity and poor tolerability driven by the PI3K-associated toxicities of infection and immune-mediated adverse events; concern with the currently selected dose and limited dose exploration; and finally, relevant findings in the PI3K inhibitor class, with multiple randomized trials demonstrating a potential detriment in OS and substantial toxicity in the PI3K inhibitor arm.

Based on the availability of new information from the updated 5-year OS analysis, an updated benefit-risk assessment of duvelisib in the current disease and treatment context is warranted. The sponsor asserts that in spite of the updated OS data suggesting the potential for harm, duvelisib may still be relevant for those in the indicated population, those with two or more prior therapies.

The FDA would like to highlight some key considerations that call into question the applicability of the results from the DUO trial to the current U.S. patient population and treatment landscape for CLL or SLL. First, the DUO trial excluded patients with prior BTK inhibitor exposure given the commonality in targeting the B-cell receptor pathway. Also, no patients received prior bcl-2 inhibitor therapy, as the DUO trial was initiated and conducted prior to the time venetoclax was approved for patients with CLL or SLL.

Nevertheless, BTK inhibitors and venetoclax now represent the current standard of care, as

they've demonstrated survival advantages, and the majority of patients with CLL or SLL will receive one or more of these agents as a part of frontline or second-line treatment.

Next, there is some uncertainty about the generalizability to the U.S. population. Notably, only 16 percent of patients were enrolled in the U.S., and there was limited representation of racial and ethnic minorities, with the majority of patients being white.

The selected control arm of ofatumumab is also a consideration in evaluating the generalizability of the DUO trial data to the current U.S. population. Ofatumumab as a single agent anti-CD20 monoclonal antibody has limited use in the treatment of patients with relapsed or refractory CLL in the U.S. Notably, the most recent version of the NCCN guidelines for CLL has removed ofatumumab as a recommended treatment option because of limited clinical use and availability.

It is also important to note that the

diseases under consideration, CLL and SLL, are indolent diseases with a long natural history and where presence of disease or progression alone isn't necessarily an indication for treatment. Per the IWCLL guideline, the indication for treatment in the first line and beyond is based on active disease, which includes specific criteria such as disease-related symptoms and progressive marrow failure.

Taking these points into consideration, the modest PFS benefit with duvelisib in the DUO trial may not translate to meaningful clinical benefit in patients with CLL or SLL, based on the indolent nature of the disease and in light of the OS data, suggesting the potential for harm. This further highlights the need for a comprehensive updated benefit-risk assessment of duvelisib, a drug with substantial toxicity concerns and a high rate of fatal adverse events, in order to ensure that we are not causing harm to patients.

It is also important to consider the currently available therapies when performing our

current benefit-risk assessment of duvelisib. Patients with CLL or SLL have multiple effective therapies with known efficacy and safety. The FDA approved treatments for patients with CLL and indolent non-Hodgkin lymphoma are shown in the table here.

As discussed, with the evolution of the CLL and SLL treatment landscape in recent years, BTK inhibitors and the bcl-2 inhibitor of venetoclax are standard of care in the front line and beyond. Given that there are no data evaluating the efficacy of duvelisib in patients who received a prior BTK inhibitor or bcl-2 inhibitor, any potential for benefit in the current population of patients requiring third-line therapy and beyond is uncertain.

When taken into context of the key issues that have been outlined throughout this presentation, this uncertainty regarding its relevance to current patients with relapsed or refractory CLL or SLL is a critical consideration in the current benefit-risk assessment of

duvelisib.

So in conclusion, duvelisib has demonstrated a potential detriment in overall survival in patients with CLL or SLL, which is consistent with the findings of other randomized trials of PI3K inhibitors. Duvelisib has also demonstrated excessive toxicity and poor tolerability compared to the control arm of ofatumumab.

Finally, the limited dose exploration coupled with the significant tolerability concerns calls into question the acceptability of the selected dose. With the availability of the overall survival analysis with 5 years of follow-up, an updated assessment of benefit-risk of duvelisib in patients with relapsed or refractory CLL or SLL after two or more lines of therapy is warranted.

We would like the committee to discuss the benefit-risk profile of duvelisib for the currently indicated population considering the updated results of the DUO trial. The voting question for the committee is, given the potential detriment in

overall survival, duvelisib-associated toxicity, concerns with the selected dose, and the safety issues with the PI3K inhibitor class, is the benefit-risk profile of duvelisib favorable in patients with relapsed or refractory CLL or SLL after at least 2 prior therapies?

Thank you. This concludes my presentation.

Clarifying Questions to Presenters

DR. GARCIA: Thank you, Dr. Telaraja.

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

Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for

my questions," so we can move on to the next panel member.

Perhaps I can start with a question to the applicant, and I apologize for my ignorance. I want to get a bit more understanding as to what -- I mean, I get a sense that you do not, based upon your presentation, number one, agree with the FDA, and number two, don't believe, based upon the data that you presented, that there is survival detriment based upon the data. And it appears that you think that it's related to the crossover effect, ofa to duve [ph], if you will.

But I want to get a bit more, perhaps, statistical understanding as to what the depletion of susceptibles really mean, and if you can dumb it down for me as to how do I interpret that, and how do I actually think of it when I look at the data. Thank you.

DR. SIDRANSKY: Yes. Indeed, I think that those are the key points I think related directly to the issue of whether there's an overall survival detriment and the overlapping Kaplan-Meier curves,

which I think, really taking us back, says it all. One of my professors always told me that you don't need statistics to tell you there's a difference; you need it tell you what the difference is. And I think that we can start from there and then move to this very important question about the depletion of susceptibles and the consequence of the crossover.

We have two great statisticians with us. Let me turn it over to Dr. Wei to help explain that.

DR. WEI: Yes, sir. Thank you. This is Lee-Jen Wei. I'm a professor of biostatistics at Harvard University. I am a consultant to the sponsor today.

The depletion process is a very interesting phenomenon, and let me just give you one example. If you think about the DUO trial and duve arm, the progression time is much longer than ofa. So think about after randomization, it takes about a one-year time point, then ask yourself, do you think the people that still have not progressed at this point, are they comparable anymore? The

answer is no because in the ofa arm, you have a lot of patients depleted because of progression.

This is a well known fact. After randomization, if the treatment effect is very good -- for example, in this case, pretty dramatic with respect to progression, then we don't have this comparability anymore. So anything we talk about after crossover, what is the effect, that's not an unbiased way to look at the data anymore.

This is well known beyond the so-called ascertainment bias. Ascertainment bias means you have a much longer time to observe deaths in the duve than the ofa. So let me stop here.

DR. SIDRANSKY: Thank you, Dr. Wei.

Dr. Makuch, do you have an additional comment to help maybe round out this question?

DR. MAKUCH: I have a few. I'll keep the remarks very brief. Robert Makuch, professor of biostatistics and director of the regulatory affairs program, Yale University. I'm a paid consultant to Secura.

Following up on what Dr. Wei said, I think

those are two very important issues. If you look at this from a very broad level, essentially we are trying to use the study design in the execution of the trial, which really must be considered when analyzing and interpreting the results. So the points that Dr. Wei just mentioned about ascertainment bias and depletion of susceptibles must be accounted for, as well as the significant crossover from ofa to the duve arm; there were 90 versus only 9.

When one does that, I think that the primary focus of the analyses should be based on the earlier part of the Kaplan-Meier curves, where you do have the primary weight of evidence. And when you do look at all those data as opposed to just the summary statistics, whether it be a hazard ratio or a mean survival time, that there you can see that the two groups are essentially intertwined with one another during the earlier part of the curves, where there is the most significant weight of evidence. And again, looking at those curves further at the tail end, there is relatively few

patients, and we all know that there's a greater amount of variability at the tail of the curves, which then gives you lesser weight of evidence associated with those later time points.

So the summary is that there are issues specific to the design of this study and its execution that you should think about when interpreting the results, and especially when looking at all the data, and especially the earlier parts of the Kaplan-Meier curves. Thank you.

DR. WEI: Dr. Sidransky, if I may just add in a couple of comments here.

In fact, last July, last year, there was an advisory committee meeting by FDA, and we had the same phenomenon we observed, this depletion problem, and the FDA statistician very nicely presented the ITT analysis, and also another one called on-treatment analysis, based on, for example, the number of deaths before progression. And he concluded very nicely that such analysis, based on this depletion process, is not valid. It's difficult to interpret. And also, a committee

member at that meeting, Professor Tom Cook from Wisconsin, also made a similar comment. So I just want to mention this is a well-known fact. It's not only unique for this DUO trial. Thank you.

DR. SIDRANSKY: Thank you very much.

DR. RICHARDSON: Hi. This is Nicholas Richardson from FDA. Can FDA comment on the question as well, please?

DR. GARCIA: Sure. Go ahead, Dr. Richardson.

DR. RICHARDSON: Thank you, Dr. Garcia.

A couple of points, one, we are not claiming that there is not a signal for efficacy here, and we discussed that there was a difference in progression-free survival and response rate. The item under discussion here today is overall survival and whether that represents a safety concern.

Now, in the allowance of crossover, we acknowledge that does impact the assessment of overall survival. The allowance of crossover does draw the hazard ratio toward 1, as indicated by the

sponsor, because the two treatment arms tend to become more similar. However, within the DUO trial, we're seeing a potential detriment in overall survival despite substantial crossover. And really what is informing this concern is that we have a higher rate of death due to toxicity in the duvelisib arm, and then in patients that crossed over from ofatumumab to duvelisib, we're also seeing patients that had a fatal toxicity.

So when you put the totality of safety data into account, even in the event of crossover, there is a substantial concern for a potential detriment in overall survival, and the crossover may be actually masking the magnitude of the difference in overall survival seen in the DUO trial.

With that, I'd like to just ask if Dr. Gormley could provide a further comment. Thanks.

DR. GORMLEY: Thank you, Dr. Richardson.

The sponsor has made a couple of statements, specifically, the overall survival findings don't support evidence of detriment, and suggestions that

there needs to be a statistically significant signal for detriment. Please note, the onus is not on the FDA to prove evidence of detriment; instead, there must be substantial evidence of safety and effectiveness, and the data that we have, that suggests a hazard ratio of 1.09, does not meet that standard.

With regards to the crossover specifically, as Dr. Richardson mentioned, the crossover by [indiscernible – audio distorted] -- here we're seeing a hazard ratio greater than 1. It could be even higher if there weren't crossover. And just to highlight this difference here, I think this really underscores that what we're seeing are concerning results with this trial.

The sponsor has mentioned several times the RESONATE trial, which was a trial of ibrutinib compared to ofatumumab in a very comparable patient population, those that are previously treated with CLL, and that trial also included crossover of a substantial amount. That trial, however, was able to demonstrate an overall survival hazard ratio

[indiscernible - audio distorted] -- ratio towards 1, so it likely could have been even lower. But we're in a situation here with a hazard ratio of 1.09, which significantly calls into question the safety and effectiveness of this product. Thank you.

DR. GARCIA: Thank you, Dr. Gormley.

Let's go ahead. Dr. Madan, you have a question?

DR. MADAN: Yes. I have one question for the sponsor and two for the FDA. But I just want to get clarification because I'm hearing mixed messaging from the FDA. Earlier in the response from the FDA, they said they were not questioning efficacy, but in that last statement, they said that there is a question about safety and efficacy.

Can I get some clarity on that? I mean, is this a safety issue or an efficacy issue, or both?

DR. GORMLEY: This is Nicole Gormley, division director. It's really a safety issue, but you can't really separate the two issues, if I can just be clear; that safety and effectiveness go

hand in hand.

If you have a toxic product but the efficacy is really substantial and it works really well, the balance then is a little bit more favorable; whereas if you have a marginal product that has substantial toxicity, it really calls into question the overall risk-benefit and safety and effectiveness of a product.

DR. MADAN: Okay.

DR. GORMLEY: So what we're talking about here is a new safety signal, but these two do go hand in hand.

I heard that I was breaking up a little bit. I just wanted to clarify. I hope you heard me. In the RESONATE trial of ibrutinib versus ofatumumab, same comparator, same comparable patient population, that also had significant crossover. The hazard ratio for overall survival was 0.43. Thanks. Hopefully you heard me clearly this time.

DR. MADAN: Okay. Thank you.

While I appreciate that safety and efficacy go hand in hand, efficacy calls into question the

need for a certain disease-specific expertise that I don't have, but I can focus on safety given what limited knowledge I bring to the table here.

So my question for the sponsor is, if I understood correctly, there was some kind of indication that there was a thought that the increase deaths were related to infections, and that is because the patients were on the treatment for a longer period of time, and when they ultimately progressed, it happened in a way that was captured as an AE related to infection and potentially lead to death.

Do you guys have any data that shows that the deaths related to infection coincided with disease progression? And that's with the presumption that I interpreted what you said correctly, so if I didn't, feel free to tell me that. Thank you.

(No response.)

DR. GARCIA: Anyone from the applicant group?

(No response.)

DR. DAVIDS: I think Dr. Sidransky may have lost his line again, so I'll wait for him to call back in. This is Matt Davids. I can start with that question.

DR. MADAN: If you want, I can redirect my questions to the FDA, and then come back to that when you guys have your communications up.

DR. DAVIDS: That will be helpful, actually. Thank you.

DR. MADAN: Okay. That's great.

So for the FDA, if we could go to slide 34, in your presentation -- and I think I was part of the PI3K discussion back in April, but I think it's important to also interpret this data in the context of this specific disease state and trial.

Did any of these other trials involve a crossover like we see in this trial for these other disease states?

DR. RICHARDSON: Hi. This is Nicholas Richardson from --

(Crosstalk.)

DR. GORMLEY: This is Nicole --

DR. RICHARDSON: -- go ahead, Dr. Gormley.

DR. GORMLEY: No. Go ahead, Dr. Richardson.

DR. RICHARDSON: Okay.

Thank you for the question regarding if some of these trials did include crossover. The answer is yes and no. In the UNITY-CLL trial that had a hazard ratio of 1.23, patients that received the obinutuzumab-chlorambucil control arm were able to crossover to receive umbralisib and ublituximab upon disease progression. So we had a similar situation with that trial as we are currently experiencing with the DUO trial. In regards to the other agents, idelalisib and copanlisib, we can double-check. I do not believe, from memory, that those trials allowed crossover, but we can double-check to confirm that.

DR. MADAN: Okay. Thank you.

Then I guess on slide 37, it was a similar list of trials with different agents, did these other trials -- again, pardon my ignorance here -- have the similar length of exposure to drug as this trial did, in terms of up to 5 years or

whatever?

DR. RICHARDSON: Hi. Nicholas Richardson again, FDA. This data here represents the monotherapy data for the respective agents based on a pooled safety population. That includes patients with CLL and indolent non-Hodgkin lymphoma. As far as the exposure, they were relatively comparable, and it ranged primarily anywhere from about 6 months to 9 months as far as the median exposure; some being a little longer than others, just depending on the characteristics of the safety population that was included for each respective agent.

DR. MADAN: Okay. Thanks.

I don't know if --

DR. GARCIA: We'll move on to Dr. Lieu.

DR. SIDRANSKY: The sponsor is back [indiscernible] -- another connection issue. I'm back on.

DR. MADAN: So I'll repeat my question for you and, again, correct my understanding if I'm wrong here, please.

My understanding is during your presentation, there was kind of a suggestion that the reason why there were some increased deaths from infection is because, ultimately, when patients with this disease progress, they get infections, and that leads to increased mortality.

I guess my question is, did you guys have any data that shows that the increased deaths related to infection occurred at disease progression?

DR. SIDRANSKY: [Indiscernible – audio distorted] -- in approximately about 40 percent. I don't have specific data to show you, but when we were looking for the cases, approximately 40 percent occurred very close to progression, but that's also known clinically, that progression, and infection, and death occur very close to one another in this refractory/relapsed setting.

I'll let Dr. Davids further comment on this because I think the real-world evidence they see I think is also meaningful.

DR. DAVIDS: Thanks. This is Matt Davids

from Dana-Farber. Yes, I certainly agree. That's what we tend to see clinically. Often in the setting of an infection, patients may have to hold a drug and may then experience disease progression, or the disease progression itself leads to increased immune suppression from an increasing burden of CLL disease, which then leads to infection; so those are very commonly associated.

I think an important point is that the patients who were still on duvelisib on this study, whether as the first treatment or in the crossover, were being very closely monitored, and all infections were being recorded. Of course patients on ofatumumab, actively on the study and for 30 days after finishing ofatumumab, were also being monitored very closely and were being recorded for AEs.

But part of this imbalance in the infections is that patients on the ofa arm who had completed treatment and were more than 30 days out from finishing that treatment, they very well probably were having infections, possibly even fatal

infections. The problem is, though, they were not being recorded that way necessarily because these patients were not being followed as closely, and some of these patients had moved on to receive other therapies at that point, which may have contributed to that infection risk. So I think it gets very challenging for those ofatumumab patients due to that ascertainment bias. Thank you.

DR. MADAN: Let me just wrap up with the --

DR. GARCIA: Dr. Madan, if you don't mind, maybe if we could actually just hold that question again, or any follow-up question that you have so we can move on to other committee members, if you don't mind.

Dr. Lieu?

DR. LIEU: Yes. Thank you. This question is for the sponsor.

In the final analysis, it's reported that 44 percent of the treatment arm discontinued the drug due to adverse events, leading to discontinuation compared to 6 percent in the control arm. So my question to the sponsor is, do

you have a time-to-treatment failure figure, or if not, can you tell us how these patients were censored or followed?

The reason I'm asking this question is because if you have a higher drop out because of poor drug tolerance, and those patients are censored before progression, then PFS could be compared among those who best tolerated the study drug versus a larger group of patients on the control arm.

DR. SIDRANSKY: Good question. [Indiscernible].

DR. GARCIA: Dr. Sidransky, it's really hard to hear you. You're breaking up quite a bit.

DR. SIDRANSKY: [Indiscernible] -- turn it to Dr. Wei, who has done the analysis.

Dr. Wei?

DR. WEI: Sorry, Dave. You're off and on. If I understand, you asked me to answer the question about treatment failure analysis.

I think this is a wonderful question. In fact, think about the situation. A patient is off

the treatment prematurely due to AE, for example, and we say, "Well, this is no good, it should be part of the risk-benefit consideration," and then the patient progressed and went off the treatment.

In fact, we did an analysis using this data from the DUO trial. We defined a composite endpoint, which included deaths, off treatment prematurely, and also progression. Then if you look at the Kaplan-Meier curve, it's dramatically in favor of duve, the duve arm, compared with ofa.

I don't know if we have this backup figure or not.

DR. DAVIDS: Can we have the slide up, please?

(Pause.)

DR. WEI: Here on the left-hand side we can say -- this is called a cumulative incidence curve. Instead of a Kaplan-Meier, actually it's almost like a 1 minus Kaplan-Meier. The curve is from zero to increasing to 1. Now, the gray curve is ofa and the blue curve is duve, and we actually considered a so-called -- very nicely you put it,

sir -- treatment to failure analysis. Look at this analysis now. The gray curve is much higher than the blue curve, and indicates, using this treatment analysis, that actually duve was performing very well. Thank you.

DR. GARCIA: Dr. Nieva?

DR. NIEVA: Thank you. Jorge Nieva, USC. My question is for the sponsor.

In the DUO trial, was there a difference in access to second-line therapies between the two arms? Thank you.

DR. SIDRANSKY: No, there was absolutely no restrictions to additional access, and that's one of the things that's really complicated to curves, and obviously the results if you keep going down the line. There was just at that time very many different regimens that were used without anything that stood out.

I'll let Dr. Davids finish because he actually ran the trial and saw these differences.

DR. DAVIDS: Yes. This is Matt Davids. I can add that I think this is a crucial point here

that hasn't come up yet, which is that most of these patients were at a time when the BTK inhibitors were just coming onto the market, so what often happened on this study is that patients with duvelisib were doing well for a long period of time, progression free, and the patients with ofatumumab would either crossover to duvelisib or they would go on a drug like ibrutinib, which had recently been approved and was available. Even in the crossover study, again, if patients went on to ofatumumab, they would usually progress quickly, and then go onto a drug like ibrutinib, a BTK inhibitor.

So one of my thoughts about why the survival has been improving very late in that ofatumumab curve is it's reflecting that access to BTK inhibitors, and that is a less relevant consideration now since these patients will have already received BTK inhibitors. So I think that's part of the effect we're seeing there.

DR. NIEVA: Thank you.

I have one question for the FDA. The issue

of ascertainment bias in collection of toxicity data has been raised a number of times by the sponsor. Can the FDA respond specifically to the problem of ascertainment bias and why it should not apply or be considered in thinking about the risk-benefit ratio? Thank you.

DR. RICHARDSON: Hi. This is --

(Crosstalk.)

DR. GORMLEY: This is Nicole Gormley. Can I just ask a clarifying question?

When you were asking, what specifically are you referring to for ascertainment bias? Are you referring to safety reports and narratives, or are you referring to --

DR. NIEVA: Yes. I --

DR. GORMLEY: -- what specifically are you referring to?

DR. NIEVA: The sponsor has posited a number of times that the reason that their drug appears more toxic is that toxicity data was collected for a longer period of time, and the background infection rate in patients with chronic lymphocytic

leukemia means that we will see infectious data occurring at a given rate over time, but because we ascertained it in one group longer than the other, it appears that there's a higher infection rate. And the FDA, thus far I've not actually heard a direct opposition to that statement as to why we should still consider the drug to be more toxic from an infection standpoint, given this issue with data collection.

So could there be a statement from the FDA as to how we should consider safety data in the setting of two different methodologies for evaluating safety in the two treatment arms?

DR. RICHARDSON: Hi. This is Nicholas Richardson at FDA. Thank you for that question. I think that's an important point, so a couple considerations.

One, as you mentioned, this trial was designed to evaluate duvelisib, which was administered continuously until progressive disease or unacceptable toxicity, compared to a fixed-duration, monoclonal antibody, so inherent in

the design is this difference.

Now, this trial was used to support registration as the agent is intended to be administered. So this is a randomized trial. It balances known and unknown factors, and when we think about the comparative assessment of safety, we're looking at safety as the treatments are going to be administered to patients. So it's really important to note this aspect because the chronic administration of duvelisib impacts that risk to patients.

So you can do the analyses both ways. You can look at it as sort of a direct comparison of the agents while they are being exposed on each treatment arm, but because of the fixed-duration aspect of the control arm, it does lead to an imbalance; however, that was the selected design by the sponsor to inform the risk of their product.

One thing that did come out of the data is that duvelisib is associated with grade 3 or higher toxicities that have a longer term onset. So when we look at the median onset to grade 3 or higher

PI3K-associated toxicities -- and this is included in the current USPI -- the median ranges from 2 months to 6 months with a really broad range of time to onset, so this chronic administration does play a direct role into the risk.

Now, it does highlight why there are differences in safety when you look at the trial overall, but at the end of the day, now we're trying to take that safety information and apply it to clinical outcomes such as overall survival, which we consider as an efficacy and a safety endpoint, and the data supports the risk or the safety concerns may be having a potential detriment in overall survival, and that's really reinforced by the fact that we're seeing fatal toxicities associated with the agents.

So as discussed, we define that as you have a fatal toxicity while on treatment within 30 days or there is a temporal relationship to study treatment. That does not include patients that have evidence of progressive disease. It does not include patients that have a window that is outside

that adverse event definition. So hopefully that shed some light on your question.

DR. NIEVA: Thank you. That --

DR. SIDRANSKY: Can I add an additional comment?

DR. GARCIA: Who is this? Please identify yourself.

DR. SIDRANSKY: David Sidransky. Can I add an additional comment to that response from the FDA?

DR. GARCIA: Sure. Go ahead, and try to be precise if you can, please.

DR. SIDRANSKY: Sure. I think the question answered the issue of how long, actually, patients are on drug for duvelisib, and again I think that's for you to consider. I think it's clear that patients are having the additional benefit, and to be clear they accumulate additional events, but it doesn't answer the issue of ascertainment bias.

I want to make it very clear that ofatumumab was given for 6 months plus 30 days, and events that normally occur were not ascertained. Per

protocol, 30 days afterwards, they happened but they were not tabulated. So you are looking at an ascertainment bias that I think cannot be negated here. It's simply that the background rates, which you saw, for example, on the placebo trial, continued to occur in these patients, but they're not tabulated.

So unlike the FDA's assertion that there are more events taking place potentially on that arm, they were basically hidden in terms of final analysis.

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

DR. GARCIA: Thank you.

DR. GORMLEY: This is Nicole Gormley. I just would like to add a comment, that also when we do time-limited analyses, we still see higher rates. I just want to highlight, with this trial design, it kind of cuts both ways. There's continued administration with one product versus a time limited with another. And yes, that sometimes can result in better efficacy for the product, but

there's also more safety. But even when we do the time-limited analyses, we also see higher rates of infection. So I'd just make that clear. Thanks.

DR. DAVIDS: This is Matt Davids. Slide up --

(Crosstalk.)

DR. GARCIA: Thank you. Dr. Freidlin --

DR. DAVIDS: Oh, sorry. Can I just make a very quick comment?

DR. GARCIA: You may be able to, actually; a comment after Dr. Freidlin asks his question, if you don't mind.

DR. DAVIDS: Sure. Thank you.

Dr. Freidlin?

DR. FREIDLIN: Yes. This is Boris Freidlin. This is a question to FDA.

It was noted repeatedly in the presentation there is a fundamental flaw in the DUO design. The design includes crossover from the control to the experimental arm in a design like this or else data are not interpretable since the trial is essentially comparing two experimental arms,

duvelisib up front versus duvelisib progression. So in a specific setting, this design could not clearly estimate potential or a detriment.

Could FDA clarify why this design is used in licensing trials? Thank you.

DR. GORMLEY: This is Nicole Gormley. I'll just start, then I'll turn it over to my statistical colleagues, if that would be helpful.

We generally discourage this design type because it does sometimes lead to more challenging overall survival analyses. The reason for doing this, though, is that from a patient perspective, there is an interest in if the patient does not do well or progresses on one arm, the desire to be on the other arm. So from a patient perspective, there is this potential advantage. It does convolute the trial design, and as such we generally discourage this because there should be, when designing trials prospectively, clinical equipoise.

As I highlighted or mentioned before, though -- and perhaps I'll turn it over to my

statistical colleagues -- I think the real issue here is that we're seeing this potential detriment despite the substantial crossover.

Could one of my statistical colleagues comment?

DR. GWISE: Yes. Hi. This is Thomas Gwise of the FDA, director of Biometrics IX.

We agree with your statement that having the crossover in such a trial design can make the data ambiguous. But as Dr. Gormley said, the onus is on the sponsor to have data that supports safety and efficacy, and having the crossover is deemed to be a benefit to the patients enrolling in the trial; they have the option to crossover. And that's it.

DR. GARCIA: Thank you.

Ms. Nadeem-Baker?

(No response.)

DR. GARCIA: Ms. Nadeem-Baker? You may be mute.

(No response.)

DR. GARCIA: Let's just go ahead. Maybe we

can proceed with the next person.

Dr. Sekeres, do you have a question?

DR. SEKERES: I do actually. Thank you.

I'm going to ask the sponsor to put up slide CE-21, and while they're doing this, I'm going to reflect a little bit on what FDA just said.

In some ways, this trial was built to win. The comparator group is ofatumumab. I think even at the time, people knew that wasn't the ideal comparator arm, given what agents were out there or were emerging, and it was given in a self-limited way. That can benefit the sponsor in looking at things like progression-free survival, but then at the same time, they have to own the fact that ongoing treatment with the drug, you have to continue to collect ongoing safety data.

If I'm treating a patient with a drug, and I give it for a year, I'm not going to ignore adverse events that emerge from the drug after 6 months because that's how I would give another drug. I'm going to continue to collect those adverse events

and respond to them, modify treatment or stop treatment, and hopefully those adverse events don't lead to death in my patient.

I think it's a specious argument to talk about ascertainment bias. It is what it is. You're giving a drug long-term; you need to collect adverse events long-term, and sometimes those adverse events will lead to death.

Is the sponsor going to put up slide CE-21?

DR. SIDRANSKY: Slide up.

DR. SEKERES: So I think the crux that we're all debating is did patients die more because they got this drug? And this is a hard thing to figure out over a 5-year period, when patients are going to switch from one drug to another.

Here we have a treatment-emergent adverse event rate with outcome of death that eventually is 15 percent in the final analysis of patients who were randomized to duvelisib. My question for you is, do you have data -- and this can go to the sponsor or the FDA -- on how many patients died from a cause other than progression, whose most

recent treatment was duvelisib, since patients bounced on and off of a variety of treatments over the course of this study?.

DR. SIDRANSKY: Yes. Thank you for the question, and I think I agree with the overall concept that you've presented. I think one of the ways that -- well, we obviously have to assess them, and I think it is important, however, to understand how long the patients are on the drug so that you are accumulating events, but is there a change, is there an increase, not just -- but also on the time that they're spending because they're benefiting from PFS.

Just before going to that -- because I'm going to pass it over to Dr. Davids since he has more knowledge about the trial and what they received -- the time that they spent on the drug is tremendously higher. The exposures actually here are -- but there seems to be a typo at the bottom. It's about 55 weeks for duvelisib and 50 for -- I'm sorry, at the final analysis and about half as much for ofatumumab. But if you look at mean times,

it's much, much higher. You go to 50 versus 75 in terms of weeks, and if you look at total times they spent on it, it actually approaches 3 to 4 times as much time as they spent on ofatumumab.

So I think it is at least fair while assessing these to take an assessment of what's happening over that period of time.

I'll turn it over to Dr. Davids, and maybe he can discuss a little bit about whether there's any information regarding other drugs and associated deaths.

DR. SEKERES: Right. That said, though, remember this is by design. You designed a study where the control arm was self-limited, so talking about differences in exposure, that's actually what you wanted. Right? And that could feed actually into progression-free survival. Patients who have a therapy and then stop that therapy are probably more likely to progress with a chronic disease like CLL than those who continue on the therapy.

So this is all by design. I think you have to own both sides of that design.

DR. SIDRANSKY: And I do. And as you said, I think -- go ahead. Sorry.

DR. SEKERES: To get back to the question, though, does anybody have data on patients who died from an event other than progression, whose most recent treatment was duvelisib?

DR. SIDRANSKY: Dr. Davids?

DR. DAVIDS: This is Matt Davids. It's a great question, and I don't know the specific number. I would say, based on the slide that we had up previously, that what we're looking at here is what's the difference between the analysis that was used for the full approval of this drug and then what has changed since that analysis; and you do see, of course, more deaths occurring in patients on duvelisib.

I think it's sort of a mix of what you said, and in our experience that some patients are dying of causes other than progression; some patients are dying of progression. There are still infections, of course, that can occur when patients are still on drug. I think the key point is that those are

all being tracked very carefully with the patients on duvelisib, and recorded, and those patients who were on ofatumumab, progressed, and went on to other therapies, are also having similar infections, but we're not tracking them, and that's why these differences seem to be apparent in the comparison.

DR. SEKERES: Yes. That's what I'm actually trying to get to, Matt. I just want to try to get the truth here.

So a patient who got duvelisib and then was treated with a BTK inhibitor, and 6 months later died from an adverse event on the BTK inhibitor, I don't think should be attributed to duvelisib. On the other hand, patients who continued on duvelisib and then developed life-threatening infection, and did die from that, I'm just trying to get to what percentage of patients that actually is in a 5-year study. I don't think you can --

DR. RICHARDSON: This is Nicholas Richardson from FDA. Can we try to address this question?

DR. GARCIA: Please go ahead if you have

that information.

DR. RICHARDSON: Sure. Can we pull up slide 13, first, from the main presentation? And then we'll have one additional slide.

From an FDA standpoint, when we look at the categories of death from a randomized trial, we utilize a standard approach. So here was the categories as presented during the main presentation. Those that are categorized as adverse events are in the absence of progressive disease. They occurred while on study treatment or within 30 days or there is a temporal relationship to study treatment. An example of that, if a patient develops pneumonia while they're on study treatment but they have a fatal event that occurs 60 days after that onset of pneumonia, we would still consider that to be related to study treatment, and it would be categorized as an adverse event since the inciting event started while on treatment or within 30 days.

The other categories represented here are progressive disease. Other represents those that

essentially do not have progressive disease or do not meet that adverse event definition, so it represents patients of what you're talking about in those that may have received subsequent therapy and may have had a fatal event, either due to a subsequent therapy or due to the underlying disease such as an infection, so they are captured here in the other category.

I think the important thing to note here, though, is in the ofatumumab arm, there were 9 patients that had a fatal event that occurred following subsequent therapy with duvelisib. So of those 28 patients from the ITT population, there were 9 patients that had a duvelisib-associated fatal toxicity that were counted as other when you just looked at the prespecified ITT population.

Hopefully that helps, and if you would like some further information on the categories of the other reasons, we can share that as well.

DR. SEKERES: Okay. Thank you. I think we can move on.

DR. GARCIA: Thank you.

Ms. Nadeem-Baker?

MS. NADEEM-BAKER: Hi. This is Michele Nadeem-Baker. I am a patient representative, and I am a CLL patient. I would like to ask questions that would go to both. The FDA pointed out that patients were excluded who had been on a BTK-i inhibitor as well, and none who were on a bcl-2, venetoclax, were included.

Here is my question. I'm unsure why the FDA did bring that up, but this would be for those who had been on 2 prior treatments. But my question to Dr. Davids or Dr. O'Brien would be, from what I understand, patients can stop responding to these drugs, and then would need a third-line treatment, but I want to make sure I understand that correctly.

DR. SIDRANSKY: Yes. I will go ahead and let Dr. Davids and Dr. O'Brien respond because that's a critical question in terms of this current treatment landscape and, in fact, the FDA was correct, that those patients were excluded in the original DUO trial.

Dr. Davids first, and then Dr. O'Brien?

DR. DAVIDS: Thanks, Michele, for a great question. This is Matt Davids.

I think a couple of important points to raise here, one is just highlighting how quickly the field has changed since this study first accrued, and it's true that now most patients who we would treat with drugs like duvelisib would be post-BTK inhibitor/post-venetoclax.

If we can do slide up. As we highlighted in the presentation on this slide -- if we can pull up the slide that's currently in the preview, please, thank you -- this is a population who, unfortunately, has a very poor prognosis. The median overall survival for this double refractory population is 3.6 months. It is true that the data so far are relatively limited for the efficacy of PI3-kinase inhibitors, but we would differ from the FDA who stated that there's no evidence of efficacy.

If we could please pull up the slide showing the PFS and overall response, so there are emerging

real-world data sets that are retrospective, but they do show potential benefits of PI3-kinase inhibitors here. This is one of the series that showed an overall response rate of 47 percent for PI3-kinase inhibitors specifically in patients who had progressed after BTK and bcl-2. Median PFS here is 5 months, which is certainly shorter than what was seen in the DUO study, but remember the median overall survival for this population is 3.6 months.

So when I'm sitting in clinic with my patients who've been through both mechanisms, I'm basically discussing best supportive care hospice or a PI3-kinase inhibitor and whether it's potential for benefit. And I tried to illustrate in my presentation some of the real potential benefits that patients can have. Thank you.

DR. SIDRANSKY: Dr. O'Brien, any additional comments?

DR. O'BRIEN: Yes. I would just say that, as Matt pointed out, this is a highly refractory group, but these are the patients we're starting to

see more and more of. In the original DUO trial, it was noted that it [indiscernible] did not have a BTK inhibitor or venetoclax. Well, venetoclax was not approved at the time, and ibrutinib had just become approved.

So yes, that population is different than this population, but this is a population that's becoming more and more common and is a big problem for us. And you might say, well, 5 months is not a really long remission, but don't forget it then allows you to bridge patients to other things. For example, in the case Matt showed, where the patient went to allo transplant, that's exactly one of the benefits of having an effective therapy that allows you to look for a more definitive treatment option going forward, for example a CAR-T or a transplant, or something like that. But this population is becoming more and more of a problem for us. Thanks.

DR. SIDRANSKY: I just would like to wrap up by saying that --

(Crosstalk.)

DR. GORMLEY: This is Nicole Gormley from FDA. Oh, go ahead, please.

DR. SIDRANSKY: No. I just wanted to wrap up and say that we're also getting some early information. We hesitate to present it here because we don't have all the data, but it looks like also in a phase 1 study in Japan, they're seeing responses after BTK inhibitors and bcl-2 inhibitors, but again it's just emerging data.

DR. GORMLEY: This is Nicole Gormley at the FDA. I would like to respond, if possible, to this, as well.

DR. GARCIA: Please go ahead, Dr. Gormley.

DR. GORMLEY: Yes. First, I'd like to highlight and underscore that we are in a data-free zone. Those patients were available at the time, but they weren't included in this trial, unfortunately. So we don't have information that's been reviewed, and we can't carve out new indications, assess the activity, or know how it would work in these populations without having data to review. The sponsor has highlighted an article

by Mato, et al., and I'll turn it over to Dr. Richardson to discuss some of the issues with that.

DR. RICHARDSON: Yes. Hi. Thank you, Dr. Gormley.

Can we bring up slide 91, please?

As Dr. Gormley mentioned, we just don't have prospective data to support safety or efficacy of duvelisib in patients that were previously treated with a BTK inhibitor or a bcl-2 inhibitor, and the information that the sponsor just highlighted, it's retrospective, it's real-world data, and there are limitations with that, so this should be interpreted cautiously. However, it did show a response rate of 47 percent, but the article does note that those responses were transient, and there was limited durability.

The other aspect is it did highlight the high rates of discontinuation primarily due to adverse events with PI3K inhibitors, and specifically with duvelisib just given the dual inhibition of gamma and delta. So again, when we

think about the ability to tolerate these agents and fill a role, we really need to base our decisions on appropriate data.

The other aspect that this slide here shows is in the second column, patients that were previously exposed to venetoclax or a BTK inhibitor received either an alternative BTK inhibitor or a subsequent, non-covalent BTK inhibitor, which are currently under development. These also showed that patients have the ability to achieve objective responses, and it was actually based on this data, higher, and it appeared to be more durable than the responses with PI3K inhibitors.

So at the end of the day, we really don't have safety or efficacy data in these patients that have been previously exposed to a BTK or bcl-2 inhibitor, so it's an important consideration, given that the sponsor has repeatedly noted that this may be a role for duvelisib, but it is a data-free zone. Thank you.

MS. NADEEM-BAKER: My question, if I could just follow up, was really based on once you use

one BTK inhibitor, if I understand this correctly, and it no longer works, then you cannot go on another BTK inhibitor; so basically, if a patient can -- it doesn't mean just because they've used one and it's no longer effective, and the next, they cannot go on another BTK inhibitor, if I understand that correctly.

Then there's --

DR. GORMLEY: This is Nicole Gormley. Sorry. Go ahead.

DR. NADEEM-BAKER: So if both of those are no longer effective for the patient, that third line would then be, as it stands now, what we're speaking of. It doesn't mean they can go back on the other.

DR. GORMLEY: This is Nicole Gormley. That was what Dr. Richardson was talking about with the second column. The middle assertion you made is not correct, and that was what their study showed. Patients can be retreated with a different --

MS. NADEEM-BAKER: No --

DR. GORMLEY: -- and have --

MS. NADEEM-BAKER: -- no.

DR. GORMLEY: -- good responses.

(Crosstalk.)

MS. NADEEM-BAKER: I would really like to have --

DR. GORMLEY: -- and a longer duration.

MS. NADEEM-BAKER: No offense, but I would love to hear from one of the doctors who's a CLL specialist on that.

DR. DAVIDS: Hi. This is Dr. Davids.

DR. SIDRANSKY: Dr. Davids, I'm going to turn it back to you.

DR. DAVIDS: Yes, I can weigh in on that --

DR. GARCIA: Dr. Davids, if you could be precise in your answer for Ms. Nadeem-Baker, that would be great. We're really behind in time, so I appreciate if you can be precise.

DR. DAVIDS: Michele is exactly correct, that if a patient progresses on a covalent BTK inhibitor, they would not respond to a different covalent BTK inhibitor, and those are currently the only approved options. That second

column reflects largely the use of non-covalent BTK inhibitors, which are still in early-phase development, and they're not available as therapies for patients in the United States. Thank you.

MS. NADEEM-BAKER: Thank you.

DR. GARCIA: Thank you all.

Dr. Crawford, Advani, and Kraus, apologies. We're really crushing with time. Maybe I'll have the three of you speak first during our discussion session.

For now, it's 11:47, so we will now take a 10-minute break. Panel members, please remember that there should be no chatting or discussion of the meeting topic with anyone during the break, and we'll resume at 11:57.

How about if we make it at 12 noon, 12:00, to start again. Thank you all.

(Whereupon, at 11:48 a.m., a recess was taken.)

Open Public Hearing

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

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment for your travel, lodging, or other expenses in connection with your participation in this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not

preclude you from speaking.

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

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

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

DR. ZUCKERMAN: Thank you. Will you please put my slides up?

I'm Dr. Diana Zuckerman, president of the National Center for Health Research. We scrutinize the safety and effectiveness of medical products,

and we don't accept funding from companies that make those products. Our largest program is focused on cancer prevention and treatments. My expertise is based on postdoctoral training in epidemiology and public health, and my previous positions at HHS, and as a faculty member and researcher at Harvard and Yale.

In April, this same committee examined six randomized trials of PI3K inhibitors used for hematologic malignancies and found that all reduced overall survival despite potential benefit for progression-free survival. FDA [indiscernible – audio distorted] findings because multiple randomized trials within the same drug class is unprecedented in oncology. That's a shocking finding that we need to take seriously, and that's the context for today's meeting.

The sponsor did a 5-year randomized-controlled postmarket study, which was 3 years longer than the data that resulted in initial approval. They found the median overall survival was 11 months shorter than the comparison drug, and

they found 50 percent of the patients died during those 5 years compared to 44 percent taking the other treatment even though that other treatment is no longer considered effective [indiscernible].

Then they analyzed patients with two or more prior therapies since that was the indication. Those Copiktra patients lived about 3 months shorter, not as bad as the larger sample but still worrisome, and 56 percent died during the 5 years of the study compared to 49 percent assigned to the other treatment.

Adverse events caused the death of 15 percent of the Copiktra patients compared to only 3 percent of the other treatment group, and the percentage of grade 3 or greater adverse events was 91 percent, and 78 percent had serious adverse events, both of these about twice as high as the comparison group. This has clear implications for quality of life, in addition to the patients not living as long.

The FDA did the right thing by requesting this postmarket study, and the sponsor did the

right thing by completing the study. Now it's time to listen to the results. We urge this advisory committee and the FDA to make it clear that approvals will be rescinded when evidence indicates that promising, short-term results are reversed based on longer term data from postmarket studies. Patients and oncologists want as many treatment options as possible, but we do patients no favors by maintaining approval for a drug that does more harm than good. As was true yesterday for other cancer treatments, the preponderance of evidence is clear today.

As a cancer survivor myself, I thank this committee and the FDA for its objective scientific analysis of the data presented [indiscernible]. I hope it will help everyone understand that an individual patient [indiscernible] specific treatment, but that treatment may not be right for the patient as well.

There are other individual differences that cause some patients to do better than others and to live longer than others. As FDA stated, these

diseases are often fatal ones. That's why large, long-term, randomized-controlled trials are so important, and help us understand which treatments are better for which patients.

There are so many problems with the data, including the very substantial changes of treatment standards that have occurred since the study was designed, a low number of U.S. patients and the dearth of non-white patients. All of these problems support rescinding approval for this indication.

It could take years for FDA to rescind approval unless the sponsor does the right thing by voluntarily doing so. Your vote today will be very influential. I hope that the sponsor will conduct new research to determine if a subgroup of patients can benefit from this drug under current treatment standards and if a lower dose is safer as well as effective; and if so, FDA should of course consider approval for a different indication. But that isn't where we are today. Thank you so much for the opportunity to speak. I appreciate it.

DR. GARCIA: Thank you, speaker number 1.

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

DR. SALTZMAN: Yes. I am Dr. Larry Saltzman. I have no financial relationships with the manufacturer. I am a 69-year-old family physician, and I was diagnosed with CLL/SLL at age 56 in January 2010. My prognostic markers included the deletion of the 13q and 11q chromosomes, as well as unmutated for IVGH [ph].

This past June 2022, a biopsy of my latest relapse of the cervical node added a 17p deletion. Upon diagnosis, I was given an 8-year end-of-life prognosis and was initially placed on a wait and watch protocol. My first treatment took place July to December 2013 with 6 cycles of rituximab and bendamustine. It was then that I left clinical practice, and I'm now involved in research regarding COVID-19 and a blood cancer's patient's response to vaccines and the virus itself.

I am speaking to you because my journey has

been complicated. At present, I am awaiting an allogeneic bone marrow transplant, and the medication that has placed me in partial remission in preparation for this event is duvelisib. My CLL/SLL has been treated and relapsed on multiple occasions. A brief summary of my treatments include the aforementioned BR [ph] regime: ibrutinib as a monotherapy, venetoclax as a monotherapy, as well as ibrutinib combined with venetoclax as a combination therapy.

I have been treated with CAR-T therapy twice. In preparation for my first anti-CD19 CAR-T therapy, as my CLL was out of control, I was treated with many cycles of bendamustine/rituximab, high-dose corticosteroids, obinutuzumab, and a fludarabine Cytoxan conditioning protocol, and that CAR-T initially worked.

Upon relapse this past February, I had a second anti-CD20 CAR-T treatment April 15, 2022, which did not work; hence, my current relapse in June of this year. As I have failed all previous therapies, it was my last hope to use duvelisib, as

I had not yet been tried on a PI3K inhibitor. Fortunately, this treatment has been working. The lymphoma in my neck, liver, and kidney are responding.

On duvelisib, I'm frequently asked if I'd developed a side effect of diarrhea or colitis. I'm happy to report that the answer is no. Perhaps that is due to the fact that in 2015, having failed ibrutinib, I needed to have the right side of my colon and terminal ileum removed due to a bowel obstruction caused by my lymphoma.

As a patient and physician, and one who has failed treatment in all classes of current CLL therapy, including chemotherapy agents, BTK inhibitors, bcl-2 inhibitors, as well as multiple immunologic CAR-T therapy, I'm hoping your decision regarding duvelisib will be one where it will continue to be available to patients like me, who have no other options. I understand there are side effects to this medication, as there are to others. Without this option, we in the CLL world may be in grave danger. Thank you for your time

and consideration.

DR. GARCIA: Thank you, speaker number 2.

We'll move on with speaker number 3. Please begin by stating your name and any organization you are representing for the record.

DR. KOFFMAN: Dr. Brian Koffman. I'm representing the CLL Society. Thank you for the chance to speak in support of the affirmative to the question, is the benefit-risk profile of duvelisib favorable in patients with relapsed or refractory CLL or SLL after 2 prior therapies?

I speak as a patient diagnosed with an aggressive, high-risk CLL 17 years ago. I'm also a retired family doctor like Dr. Saltzman and the co-founder chief medical officer and executive vice president of the nonprofit CLL Society dedicated to the unmet needs of the CLL community. I have committed my last 15 years as a physician, educator, retired professor, advocate, and patient to understanding, researching, and explaining not only the rapidly changing therapeutic landscape, but also ensuring that both patients and providers

are up to date, and that all stakeholders are aware of what matters most to patients.

To that end, I'm going to share some results of our survey of 1147 CLL patients presented at ASH, the American Society of Hematology's annual meeting. The most important factors in selecting treatment and its statistically similar 9 out of 10 patients in our study was response rate, overall survival, and progression-free survival. Risk of immediate side effects, while still very important, was less of a concern than cost or insurance issues. In summary, PFS, OS, and ORR are equally important to patients, and more important than toxicity.

FDA shared possible multiple effective therapies. Let's review them from a patient's perspective. While CLL is heterogeneous in its presentation and progression, it is not always indolent and can be aggressive, as it was in my case. About 80 percent of us will need treatment. That is proven for the majority of us.

We have two superior outcomes, a bcl-2

inhibitor and the BTK inhibitors. After a patient has failed by the one and only approved bcl-2 inhibitor, venetoclax, and I want to emphasize this, any one of the approved or off-label BTK inhibitors -- because if you progress on one, you will progress on the others -- they all bind at the same site and have the same sensitivities. Additional choices are limited, the prognosis is poor as you've heard, and survivability is measured in months. Moreover, when a patient runs out of these approved options, the last few months of life for many CLL patients consist of numerous complications and overall low quality of life often spent in hospice care.

The role of chemotherapy, which was on that list in the relapsed/refractory setting, if any, is diminishingly small. Guidelines have shifted away from the use of chemotherapy, which generally combined an anti-CD20 antibody with a purine analog or alkalizing agent.

Additionally, after being failed by 2 lines of therapy, as Dr. Saltzman's case demonstrated,

many patients have acquired mutations in TP53 that would render CIT largely ineffective. Further, avoiding chemotherapy is a factor in choosing therapy in over half of the patients that we survey. The use of monoclonal antibodies on that list is generally not recommended due to their poor outcome. If duvelisib is no longer available, that leads only to PI3-kinase idelalisib for use with rituximab. Anti-CD20 antibodies have been proven to severely dampen vaccine response and lead to poor outcomes in patients with SARS-CoV-2 infection, something to consider.

One of the best alternatives for patients in this circumstance is the clinical trial. Sadly, for a variety of reasons, the clinical trial may not be a possibility due to inclusion/exclusion criteria, cost, and geography. Moreover, there is historical distrust of clinical trials, particularly in marginalized communities of color.

Based of few viable treatments, the ability to use duvelisib as a single oral agent that does not require the use of an immunosuppressive IV

monoclonal antibody is welcomed. While the toxicities of duvelisib should not be discounted, it must be aggressively and proactively managed. Its use remains an option to be discussed between an informed patient and their doctor as part of a shared medical decision making.

Duvelisib is an active drug for those with relapsed/refractory CLL, as proven in phase 3 trials. Frankly, our research tells us that the questionable statistical lack of overall survival advantage, while not to be ignored, would not be a deal maker for most patients. By the way, the crossover in the RESONATE trial, ibrutinib versus ofatumumab that was referenced early, was a late trial modification after the overall survival curve had significantly separated, so comparison with DUO is fraught. The CLL Society encourages crossover to ensure clinical equipoise. Trials are for patients, not the other way around.

Many CLL patients on duvelisib may not only be trying to control their disease -- for a short period of time as they move towards a transplant or

other therapies, making their time on medication short. For others, duvelisib has provided a charitable benefit for many. From the patient's perspective, despite its toxicity, the answer to this question of risk-benefit of duvelisib being favorable is a resounding yes.

Despite progress, CLL/SLL is not a solved problem, and we patients need more safe and effective therapies. Please note, the CLL Society and other advocacy organizations are willing to spend whatever time it takes to help find a safe path to keep duvelisib available, and at the same time ensure that its serious adverse events are properly addressed. Thank you for your consideration in keeping us safe in our incurable disease, controlled at all stages.

Clarifying Questions to Presenters (continued)

DR. GARCIA: Thank you, speaker number 3.

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 take the prerogative as the

chairperson of the meeting. I know there were three pending clarifying questions from Dr. Crawford, Dr. Advani, and Dr. Harrington. So if you three can be precise with your questions to either the applicant or the FDA, or both, we can try to tackle those three questions in less than 10 minutes so we can move forward with the discussion question, if you don't mind.

Maybe we can start with Dr. Crawford.

DR. CRAWFORD: Thank you, Dr. Garcia.

Before the break, several raised questions regarding the adequacy of the DUO trial design and ability to interpret results. My question to the sponsor is on a different direction related to trial design and adequacy.

I very much appreciate the brief comments made by the sponsor regarding the importance of real-world evidence. In that vein, I revisited some comments made by FDA and speaker number 1 during the open public hearing. In their presentation, the U.S. Food and Drug Administration noted applicability of the DUO trial to a U.S.

population in that only 16 percent of the patients were enrolled in the United States and over 90 percent of patients were white.

In the sponsor's briefing documents that were made available to us, table 2 shows baseline demographics for the ITT population and labeled indication population. For the duvelisib arms, 94 and 95 percent of patients enrolled were white; respectively, for the ofatumumab arms, 89 and 92 percent were white. In the entire DUO trial, fewer than 1 percent of enrolled patients were black. The race of others was either unknown or not reported.

Race and ethnicity may influence overall survival for CLL for a variety of reasons, so I ask the sponsor to comment on the representativeness and generalizability of results of the DUO trial for us.

DR. SIDRANSKY: Before I turn it over to Dr. Davids, we share always, and I personally share, those concerns. I think it's something that we need to grab always in terms of having as much

inclusivity as possible. I think, by the way, it's one of the issues that concerns us, that with the long list of drugs that are historical and have very little activity beyond duvelisib, to basically point patients only to clinical trials, as Brian Koffman just mentioned, also leads to potentially some imbalance in terms of being able to accrue these patients, so I think we all have to do more in recruiting them.

But I'll hand it over to Dr. Davids, who was involved with the trial, and I'm sure did everything possible to enroll as many minorities as possible.

Dr. Davids?

DR. DAVIDS: Hi. This is Matt Davids. I'll just comment briefly on this. First, in terms of the question of patients coming from Europe versus the United States, the patient populations are overall very similar between the two geographic areas. We very frequently collaborate with European colleagues, and in fact there are examples of drugs approved in CLL with largely

European-based studies.

Second, with regard to race, certainly there were efforts made to recruit underserved minorities on this and all of our studies, and that is very important. I will note that genetically, CLL is more common in Caucasians, and that certainly does contribute to the limited enrollment of underserved minorities. Thank you.

DR. SIDRANSKY: Thank you for the question.

(Pause.)

DR. CRAWFORD: Thank you for your response.

DR. GARCIA: Thank you for the question. Sorry. I got disconnected.

Dr. Advani, you had a question?

(No response.)

DR. GARCIA: Dr. Advani?

(No response.)

DR. GARCIA: Dr. Advani, you may be on mute.

DR. ADVANI: Can you hear me now?

DR. GARCIA: Yes, we can. Please proceed with your question.

DR. ADVANI: Yes. A lot of it was already

answered by the real-world slide, which was presented, but I just have one other question for the sponsor, please, which is, on the lower doses in your previous experience, was the rate of infectious deaths similar or lower, on the lower doses?

DR. SIDRANSKY: I'm going to go ahead and direct it at Dr. Davids to answer the question.

DR. DAVIDS: Thank you for the question. Although the numbers of patients are, of course, much smaller on the lower doses, since those were from the phase 1 study, there was no apparent difference in the rate of infection compared to the much larger data set for the approved dose in the larger studies.

DR. SIDRANSKY: And I just want to wrap up with dose that when we talk about dose, one of the things today that's common is to talk about dose interruptions or dose holidays for these kinds of drugs, and those aren't always easy. It's not just about just increasing dose, but also trying to prescribe dose holidays into trials because

afterwards, one must look also at the ability of patients to stay on that kind of regimen; and stopping all the time, especially for elderly patients, that can be very difficult. Thank you.

DR. ADVANI: Thank you.

One more question is, when you have data from this trial on when -- like some of these infections and the infections that peak, is it after -- I know this was a 5-year study, but do you have a hint that nothing happened before 2 years or 3 years, and then all starts happening much later, or was there a gradual increase over time?

DR. SIDRANSKY: Actually, when we bin the data -- that's a good question -- we see that at the beginning there was a slight increase compared to the trial continued, but it continued to accumulate. And the only thing we really see is that after about 24 weeks, when you essentially have completed the ofatumumab and everybody's essentially crossed over to duvelisib, that they just continue to accrue at about the same rate in the duvelisib patients. So I would say that it

remains pretty constant and, again, it doesn't change much over time. Thank you.

DR. ADVANI: Thank you.

DR. GARCIA: Thank you.

And finally, Dr. Harrington, final question?

DR. HARRINGTON: Thank you.

I think that we can all agree that because of the design, it's very difficult to evaluate the long-term effects on both survival and some of the toxicities because of the ascertainment bias, so that to me makes the quality of the time progression free important, and particularly important from the patient's perspective.

I think we heard mixed messages from the sponsor and the FDA about the quality-of-life data that was gathered in the study. I think the FDA, to summarize if I get it correctly, said it wasn't particularly reliable, it wasn't relevant, and the sponsor at one point said that the quality-of-life data was favorable.

So I'd like to hear just a little bit more from either the FDA or the sponsor, are there

reliable data, patient-reported outcomes, and if not, should we just set that question aside and base this purely on the hard measurements?

DR. SIDRANSKY: I really much appreciate that question because I think that time and effort was done to assess this, and as we know in many trials, it is not.

Slide up. Before I hand it over to Dr. O'Brien and then Dr. Davids, I do want to show you the slide, and you can start reading it as Dr. O'Brien will first describe, then Dr. Davids. But I think the time and effort went in to see it [indiscernible], and I think it's very favorable for duvelisib. So slide up, and Dr. O'Brien first, and then Dr. Davids.

DR. O'BRIEN: Yes. It's true that these quality-of-life measurements are not specific for CLL patients, but they're certainly very well accepted quality-of-life indices, and you can see here they are clearly favoring duvelisib.

The other point I want to make is even in the relapse setting, if a patient relapses but

they're on a trial and we're following them carefully, they may be left with very little disease. The point is, we do not treat patients until they become symptomatic, so every patient going on the DUO trial would have been a patient who is having symptoms and there were problems related to their CLL, or they wouldn't have received any treatment at that point in time. So I think it's really important to point out that these are all symptomatic patients, and clearly the quality-of-life measures that you see there seem to favor duvelisib. Thank you.

DR. SIDRANSKY: Dr Davids?

DR. DAVIDS: Yes. I fully agree with that. I would just add, both related to patient-related outcomes, as well as the onset of AEs, because there are appropriately a lot of questions around that from the committee, I think it is important to be comparing apples to apples.

Really, I think the focus on the first 6 months, comparing duvelisib and ofatumumab with respect to both the patient-related outcomes and to

the AEs, it is informative. And yes, during that comparable period, you do see somewhat higher risks of various AEs with duvelisib, but you also see the benefit.

So this is really about the benefit-risk, and that's why we believe that duvelisib is a valuable option. That's why when this was just discussed by the NCCN panel, they agreed with that, so that's what I would say about that question. Thank you.

DR. SIDRANSKY: And I couldn't have said it any better. Thank you.

DR. GARCIA: And perhaps we could hear from the FDA. Thank you.

DR. GORMLEY: Hi. This is Nicole Gormley. We'd like to respond as well.

I'll start before turning it over to some of my other colleagues. But just to mention, specifically, we really value having the PRO data because, generally, it can provide really meaningful information about the patient experience. In cases or situations like this, it

has the potential to be done and provide meaningful information. Unfortunately, in this specific trial, the data collected has limited relevance and was not supportive.

I'll turn it over to Dr. Richardson to comment further.

DR. RICHARDSON: Hi. Thank you, Dr. Gormley. Nicholas Richardson, FDA.

As mentioned, we actually commend the sponsor for capturing PRO within the trial because it can inform toxicity and tolerability. However, when we looked at the instruments that were used, the EQ-5D, as Dr. O'Brien mentioned, it's not specific for CLL, and it's a generic instrument, so the items really weren't relevant treatment-related symptoms, items that could inform toxicity and tolerability. Then when we looked at the other item, the FACIT-F, there was no observed benefit when we looked at that measure either.

So because of some of the limitations of the measures that were used, we weren't able to effectively utilize this data when we assessed

toxicity and tolerability from the DUO trial.

DR. HARRINGTON: Thank you.

Questions to the Committee and Discussion

DR. GARCIA: Thank you all. I think we're going to move on.

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 proceed to ask these questions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at a specific request of the panel.

So the question for the committee to discuss seen here is for us to review and discuss the benefit-risk profile of duvelisib for the currently indicated population considering the updated results of the DUO trial.

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

(No response.)

DR. GARCIA: If there are no questions or

comments concerning the wording of the question, we will now open the question to discussion. And perhaps I can just start by asking the committee, unless you have a very important question to ask FDA or the applicant, we should probably just try to take advantage of the time to actually have a robust discussion, based upon the data that we have heard and the documents given to us in the docket.

Mr. Mitchell, I see you have a comment.

MR. MITCHELL: Yes, I do, and really I want to ask the rest of the ODAC to help me here.

I'm hearing two distinctly different things from a lay person's perspective. One is that the overall survival data are confounded by crossover and everybody agrees that that is true. However, the FDA says that the overall survival is being affected by severe adverse events. When we talked about is it a safety issue or is it an effectiveness issue, the FDA said, essentially, it's a safety issue; then used to back up that core point, it presented the safety profile of other drugs in this class.

I'm still struggling to figure out what those conflicting positions mean from a statistical and a data analysis perspective, and it would be very helpful to me to hear from the trained members of the ODAC to untangle those conflicting points.

DR. GARCIA: That's a great point, Mr. Mitchell. I think that we have a statistician on our roster today, so I wonder if we can perhaps start with that.

Dr. Harrington, maybe you can help us out?

DR. HARRINGTON: I just came off mute.

Mr. Mitchell, could you repeat that for me just one more time? I know it is the distinction between whether it's a safety endpoint or efficacy endpoint.

MR. MITCHELL: It's two things. The sponsor says that the overall survival benefit is being confounded by crossover. The FDA says, okay, we know that there's a problem interpreting this research design because of the crossover, and someone along the way asked the question, "Well, is the overall survival being affected more by

efficacy or by adverse events, safety?" And the FDA said the issue is really about adverse events and safety, and then presented to support that, the safety profile of other drugs in this class.

So is there an advantage on overall survival even if we can't tease it out completely because of the crossover challenge? And really, is the question before us more about is this a safe drug for people to take?

I'm having a hard time wrestling with that. I don't think that the discussion so far today has given me a clear answer to that as a lay person, so I'm seeking help from those of you who are trained.

DR. HARRINGTON: It's a great question. It's right to the heart of this, and difficult to evaluate precisely.

I think that where I'll begin, and then perhaps Dr. Freidlin would want to jump in as well, the potential detriment in survival in the estimates are not something that we can rely on because of the confounding, so we really don't know what the long-term effect of survival is for this

agent compared to ofa, because that comparison was confounded.

So the sponsor has spent some time trying to show us that it's not due to adverse events that are caused by the drug. I remain unconvinced of that because there clearly were lots of episodes of infection that led to death, lots of serious infection on the duva arm.

So I can't tell you exactly how to tease out what is caused by infection and what is caused by effectiveness of the drug. I can tell you that, for me, the signal leans toward the fact that these side effects of the duva are potentially dangerous and certainly lead to either decreased survival or treatment that is compromised in the long run, which ultimately might lead to decreased survival.

So I'll stop there and see if others want to add to that.

DR. GARCIA: Perhaps, Dr. Freidlin -- I know you have your hand raised -- can help us.

DR. FREIDLIN: Yes. Just to clarify, the question is, is there excessive mortality or

detriment on survival for the experimental arm relative to the standard of care? And because of the crossover in this trial, the trial cannot really address this question because the control arm is not standard of care anymore because the patients started ofa, and then crossed to the experimental agent.

So that basically makes an unbiased evaluation of the survival detriment enforceable, and what you see is that there are 90 patients who crossed from the control to the experimental arm, and nine of them had treatment-related mortality. So that by itself potentially biases down the estimated detriment because you have -- well, again, I cannot guarantee that, but theoretically those 9 deaths should be removed from the control arm because that wouldn't happen if the patients hypothetically wouldn't get the drug.

So we have a biased estimate of relative mortality, and that's why I have an issue with this design. It's impossible to estimate for sure. FDA presented a model which suggested that, I believe,

the hazard ratio could be as high as 1.22 for survival, but it's a model based on assumption. So there is no really way for this design to provide an unbiased estimate of mortality detriment. That's it. Thank you.

DR. GARCIA: Thank you, guys.

Dr. Nieva?

DR. NIEVA: One of the things that maybe we can talk about to get at Mr. Mitchell's question is really how well can we look at overall survival in a chronic disease more than 3 years after a therapy is given, because that's really where the overall survival curves really start to cross.

When you step back and look at those curves, they're really not different, and I think when we're talking about chronic diseases, looking at overall survival for safety signals is problematic unless it's obvious. And I think in this case, there's not an obvious overall survival issue. We're not seeing a bunch of people suddenly die on the therapy and seeing the survival curves widely split. So when I see these survival curves and I

see them effectively overlapping, I think to some degree it's reassuring.

Back when our cancer patients survived 6 and 12 months with most of their advanced diseases, I think overall survival was a great metric. But now when patients are getting 3, 4, 5 subsequent therapies, after the therapy that was given in the clinical trial, I think it's really hard to get at overall survival and trying to blame it on the therapy that was given 3 therapies before.

So I see the main issue here being, does the drug work against the disease? Is there an obvious upfront toxicity signal? Is that safety signal manageable or is it particularly problematic? And I think that's how I would look at this and try to interpret the data we've seen. Thank you.

DR. GARCIA: Thank you, Dr. Nieva.

Just to expand on that, I think that although I do agree with that statement, for me it's somewhat hard to look at this data and separate this data with the other class of agents. You may recall we had an ODAC meeting back in

April, where we really addressed the concerns with dose optimization, safety, and perhaps survival detriment with the class of agents, PI3K inhibitors. And although it may be unfair to some extent to lump the DUO data into all those other trials, the reality of it is, it's just hard to ignore. Right?

There is no doubt that patients need a third-, fourth-line therapy, but the reality of it is, I'm also questioning if you get a BTK first, and then you get a bcl-2 inhibitor later, if you go on a third-line setting, there is really no prospective data demonstrating that this agent or the PI3-kinase agents are, in fact, the right agents.

One has to wonder that if we were to develop a clinical trial -- and again, I'm not a CLL expert -- today, if we didn't have a PI3-kinase approved in this space, how would one develop such a trial? One perhaps will say, I will allow patients to have failed prior BTKs, prior bcl-2's, and then randomize patients to what? To duvelisib,

against what? What will be the control arm in those trials?

So I think for me, the question has been, how do you put this data into the general context of what I have seen as potential detrimental outcome with the PI3K inhibitors in this patient population, with a very long natural history, I may add.

Dr. Madan, do you have a comment?

DR. MADAN: Yes. I just wanted to say that I think Dr. Nieva crystallized my perspective on this very well. And, Mr. Mitchell, this is a very complicated thing, and you are not alone in trying to figure out an obvious answer, because I don't think there is one.

But let's come back to this whole class versus the specific question we are being asked today. I think it's important to focus on this trial because I was part of that ODAC in April as well, and it was a more general conversation. But when you dial down into the specifics, you could see why there's an overall survival question here

in this particular trial.

So for me, I'm hard-pressed to rely on a class effect as being a tiebreaker in a situation where I think there's very clearly a lack of definitive data on either side of this. I feel like, for me, when I look at this data, I interpret it within the context of the toxicities we're seeing, the disease state, as opposed to a broader class effect where other agents may target, in theory, the same pathway, but the off-target effects may be very different and have other types of toxicities.

The other thing I'll say, just to kind of build on what Dr. Nieva said, is we're kind of looking at deaths related to treatment, or deaths on treatment, that are separated by years, with the control arm being a short-term treatment and the experimental treatment here being a long-term treatment, so they're separated often by the ultimate natural history of the disease. And for me, again, that's hard to really isolate what is treatment related and what is ultimately inevitable

of disease progression. So I just thought I'd put that out there.

DR. GARCIA: Thank you, Dr. Madan.

Dr. Sekeres?

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

This is complicated, and I think it's complicated, as the FDA indicated earlier, because of the study design. You have one arm that's self-limited for about 6 to 7 months of therapy, and then another arm that's given ad infinitum. Then we're expected to try to figure out how many of these excess deaths were due to duvelisib alone versus subsequent therapy. And when I tried to get at this earlier, the FDA did show a slide that very specifically identified adverse events that were treatment related to duvelisib that were in excess.

So I look at this, and also I'm reflecting on what you said, Dr. Garcia, about what's essentially the totality of data of this class of agents, which shows that there's a problem here. These drugs do have toxicities, and we're willing to accept a certain amount of toxicity for

extraordinary benefits with life-threatening diseases.

What I'm not seeing is the equation for that totality of data really adding up here. We're seeing what appear to be excess toxicities that are very specific to this class and are reproduced in different members of this class. We're seeing a progression-free survival advantage that may have been jump-started a bit by the trial design itself, where you have one drug given continuously and another drug given only for a shorter period of time, and then stopped, and we're not seeing an improvement in overall survival.

Progression-free survival, at least in my mind, is not the end game. The end game is improvement in overall survival. Progression-free survival gets us there, particularly with chronic diseases where people are going to live years with them. So here we actually have the 5-year follow-up, and we don't see an improvement in that overall survival. We do see excess toxicities. And I just think we have to remember the end game

itself is not the progression-free survival; the endgame is overall survival. And you can argue about the lack of significance of the excess death rate, but I don't think you can argue that in the end, duvelisib is allowing people to live longer, long term.

DR. GARCIA: Thank you, Dr. Sekeres.

Ms. Nadeem-Baker?

(No response.)

DR. GARCIA: Ms. Nadeem-Baker, you may be on mute.

MS. NADEEM-BAKER: [Inaudible] -- for patients. Can you hear me now?

DR. GARCIA: Yes. Please go ahead.

MS. NADEEM-BAKER: For patients, we're not talking this is frontline therapy, nor secondary therapy. This would be when both of those have failed, if I'm understanding this correctly. This would be the third line of therapy, and given that, for some patients, many of them, this could mean life or death to begin with.

So that is how I'm thinking about this, but

I may be thinking about that incorrectly, but it does seem that way, as the two other classes of drugs that are mostly used now, if they had been exhausted, then this would be the third line of therapy. And again, it's a chronic disease; it's very complicated.

So for the patient experience, I think if it would be a life or death decision, and if patients are educated by their doctors before they would even go on duvelisib, and I believe that's already in the REMS, maybe boost that up a bit on what's required -- and again, this is, of course, in patient, layman's language on my part -- and it would be an option for patients to live longer.

DR. GARCIA: Thank you.

Dr. Kraus?

DR. KRAUS: Yes. Thank you, Dr. Garcia. Albert Kraus, industry representative.

It is a very complicated situation. Truly on the safety level, I just want to remind this drug has full approval in an indicated kind of refractory setting, so this is about whether it

could cause harm, not about did they confirm benefit, which most of you obviously know, but I just thought I'd clarify that -- quite different than some discussion -- and whether it causes harm versus we didn't rule harm out.

Obviously, safety is critical and survival is the ultimate endpoint, assuming you can achieve it without making it so bad on patients they don't care about an extra little time. But one of the things here is balancing it, and I think it was just stated, is this ability to treat patients who have alternatives within the indication and also potentially lengthen their life, and give them other alternatives, time for other drugs, or other treatments.

One of the things -- and this will go back, and I'll probably cycle back to Dr. Harrington at the end -- is I'm struck with this is a design in the trial that doesn't tell you much about OS, in my view. It's duva versus duva -- or ofa followed by duva. And if I go back to how we look at data for many different trials, if we were here talking

about efficacy, and we had instead of a 1.06 hazard ratio with 92 percent on confidence, and 0.71 to 1.58, if we're talking about efficacy and we say "Gee, we have a 0.94 hazard ratio; we think it's a benefit," and the hazard ratio is 0.71 to 1.58 or thereabout, I think everyone would kind of laugh us out of the room, and FDA would say, "Absolutely not. We don't know that's anything different than 1, or maybe worse."

So this presumption that we have evidence from this trial that there's a hazard, I think we have to be careful statistically about that. So I would ask Dr. Harrington to speak to that premise. I understand, and I thought the discussion around taking it back to treatment-related toxicity and death is a valuable one because you can kind of see it related to treatment during a time frame. But the overall OS state is so confounded in so many ways here -- subsequent therapy, et cetera -- with these hazard ratios, I don't know why we think there's hazard from those numbers, to be honest.

So I'd ask Dr. Harrington, if you get a

hazard ratio of 1.06 or 0.94 with these kind of error bars, is that point estimate to be believed is different than 1?

DR. HARRINGTON: So that's a great question. To answer that question directly, no. When you have a wide confidence interval, that point estimate could bounce around in a fairly large range of values. I think even more to the point here with this trial is that even that estimate and its confidence interval, the uncertainty is not in how precisely that was measured; the uncertainty really is in the confounding that was induced by the design. In other words, that hazard ratio could be completely wrong. And as Dr. Freidlin pointed out, it's very, very difficult to make it right given that we're faced with only the data from the design.

I think my statistical intuition here is that it would not be right to view this therapy as a third-line option that would extend life. A couple of people have pointed out maybe this is a good option for patients in third line who want to

live a little bit longer. I think the data suggests that this might be a good option where you might get some additional progression-free time, but the data do not at all support a claim that this would extend life.

Now, that's different, of course, than what the FDA and the sponsor have addressed here, and that's whether it's harmful and whether there's a survival decrement. We can't say that there is, that's an answer that no one likes to hear, but it's very, very hard to say reliably here, based on the trial data, that this is causing an increased death rate.

So for me, as others have pointed out and Dr. Garcia does, I rely on the data that comes from the class of drugs, which says a potential survival disadvantage here has been seen in several similar agents across trials. So while we don't have a confirmed survival decrement based on this design, I think we're forced to use external data that's from those trials.

So I am certain you cannot say, as I said

before and I'll stop, that this is a third-line option that will give patients a little bit longer to live, but that I think is fairly clear.

DR. GARCIA: Thank you.

I have to say that I have been informed that the public has lost access to the meeting, and therefore since it's a public meeting, we will have to take a 5 to 10-minute break until we allow the public to have access to our discussions. So please stand by. Our DFO and technical team are working behind the scenes to have the public reconnected, and we can rethink our discussion and conversation when we left it. Thank you.

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

DR. GARCIA: I understand that YouTube is experiencing international outages that are impacting live streams all throughout. An alternative link has been posted on the YouTube webpage, and an alternative link is also being posted on the FDA meeting notice page.

Dr. Chen, can we start again or at least

getting back to our discussion?

DR. S. CHEN: Thank you, Dr. Garcia. This She-Chia, the DFO. Thank you all for your patience. Yes, just momentarily, we'll switch to the discussion question page, and then we can start from there. Thank you.

DR. GARCIA: Thank you.

Alright. I think we all are hoping that the public has been able to reconnect in the new links provided, and we've been, again, reviewing and discussing the benefit-risk profile of duvelisib for the currently indicated population considering the updated results of the DUO trial.

Dr. Harrington, I don't want to steal your thunder or speak for you, but Dr. Harrington was just summarizing some of the challenges with the clinical trial design and the inability with that design to be able to actually demonstrate with certainty any potential detriment in overall survival, based upon the DUO trial.

So perhaps we can move on to Dr. Lieu.

DR. LIEU: Thanks so much. I'll try to make

this relatively quick. I just want to point out that I certainly agree and appreciate Dr. Nieva's point about if you have an indolent disease, and overall survival, obviously, is very difficult to figure out in that setting, then you become more compelled by overall response rate and progression-free survival. I think the progression-free survival benefit here is compelling and certainly appreciate Ms. Nadeem's point that we want more drugs in this setting. We don't want to sit in front of patients and tell them that we have nothing to offer them.

I do want to make the mention of this point, though, and that is the bar that we set and the toxicity we expect our patients to be able to handle or tolerate in a setting where you have either an aggressive disease or an indolent disease. If you have a disease where survival is measured in weeks to months, the bar that you set for toxicity and what you're expecting out of a therapy is pretty low, then that setting would expect or be able to tolerate I think a lot of

toxicity.

But the flip side is also true. If you have an indolent disease, what is the cost to our patients that we're going to expect out of a therapy, in a setting where we're not sure that it improves overall survival? I just bring this up because in the duva arm, the treatment-emergent adverse event rate was 14 percent in terms of a rate of death, and that's not insignificant, and that's an incredibly high cost.

One of my concerns is that -- and I'm sure there are patients that are alive and that are well today because of this treatment, but we also know that the flip side is true, and I think that's what makes this decision so difficult, is that there are patients that have passed away because of this medication. So it's not just about offering treatment options and seeing the response rate, which I think is impressive, but also the cost in terms of toxicity, and in this situation, death. So the concern here is that you may have deaths related to not only disease but actually treatment

here, and I think that that's the concern that we're facing.

DR. GARCIA: Thank you, Dr. Lieu.

Dr. Chen?

DR. A. CHEN: Thank you. I just wanted to comment that CLL is not always an indolent disease. In this situation at third line where it's relapsed or failed bcl-2 inhibitor and BTK inhibitor, it's much more aggressive, so the toxicities we may be willing to accept are higher. And that's where the sponsor has been pitching this, but there is actually very little data to suggest much efficacy of this in that setting. There aren't any large series, so it makes this decision difficult. And I would agree with some of the other comments that the overall survival, the detriment is relatively small and the hazard ratio crosses 1, which makes it very difficult to interpret. Thank you.

DR. GARCIA: Thank you.

Dr. Freidlin?

DR. FREIDLIN: Dr. Harrington already made my point. Thank you very much.

DR. GARCIA: Thank you.

Dr. Madan, you have another comment?

DR. MADAN: No. Sorry. I'll take my hand down.

DR. GARCIA: Dr. Sekeres?

DR. SEKERES: No. Sorry.

DR. GARCIA: Alright. Perhaps I can summarize some of our discussion. I appreciate everyone -- despite of the technical difficulties, I think we were able to brainstorm a bit.

Clearly, let me just start by saying that all of us feel that this is a complex situation just by virtue of the design of the clinical trial. Some of the themes of our discussions really relate to our inability of using this clinical trial design to really determine the true potential detriment in outcome on patients receiving duvelisib, and clearly that it relates to the confounding effect of crossover.

Some committee members also talked about the challenges of the trial design just by virtue of thinking of the trial as frontline duvelisib

against sequential duvelisib, if you will, and equally important, whether or not duvelisib is in fact the right agent in the third-line setting after patients get contemporary therapy with BTK inhibitors and/or bcl-2 inhibitors, for which right now is a pretty open space, and there's no prospective data, at least level 1 data, suggesting its activity in that space.

There were comments related to the concerns of significant treatment-related AEs, some of which could lead to death in the duvelisib arm, and what we probably related to excess toxicity and the inability to really know if they were related to true treatment effects or progression of disease while they were on treatment or in subsequent therapy.

There were comments related to specifically that the end game for our clinical trials in this context is not PFS, but rather overall survival. Clearly, it is hard to look at this data in the absence of the clinical data that we have had with all PI3-kinase inhibitors as a class effect, if you

will, in these diseases that are chronic in nature, that have a long enough natural history, recognizing that some patients may not have that long natural history. So it has been, obviously, a complex discussion, and I predict that it's not going to be an easy vote when we come to that process.

If there is no further discussion on this question, we will now begin the next question. We will now move on to question 2, which is a voting question. Dr. She-Chia Chen will provide the instructions for the voting.

DR. S. CHEN: Thank you, Dr. Garcia.

Question 2 is a voting question. Voting members will use the Adobe Connect platform to submit their votes for this meeting. After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

If you are a voting member, you will be moved to a breakout room. A new display will

appear where you can submit your vote. There will be no discussion in the breakout room. You should select the radio button that is the round circular button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected. Please note that you do not need to submit or send your vote. Again, you need only to select the radio button that corresponds to your vote. You will have the opportunity to change your vote until the vote is announced as closed. Once all voting members have selected their vote, I will announce that the vote is closed.

Next, the vote results will be displayed on the screen. I will read the vote results on the screen into the record. Next, the chairperson will go down the roster and each voting member will state their name and their vote in the record. You can also state the reason why you voted as you did, if you want to.

Are there any questions about the voting process before we begin?

(No response.)

DR. GARCIA: Question 2 -- I've displayed the voting question -- is a long question, so I'm going to read it.

Given the potential detriment in overall survival, duvelisib-associated toxicity, concerns with the selected dose, and the safety issues with the PI3-kinase inhibitor class, is the benefit-risk profile of duvelisib favorable in patients with relapsed or refractory CLL or SLL after at least 2 prior therapies?

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

(No response.)

DR. GARCIA: If there are no questions or comments concerning the wording of the question, we will now begin the voting on question number 2.

DR. S. CHEN: We will now move voting members to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. S. CHEN: The voting has closed and is

now complete. Once the vote results are displayed, I will read the vote results into the record.

(Pause.)

DR. S. CHEN: The voting has closed and is now complete. The vote results are displayed. I will read the vote totals into the record, a total of 4 yeses, 8 noes, and zero abstentions.

The chairperson will go down the list and each voting member will state their name and their vote into the record. You can also state a reason why you voted as you did, if you want to. Thank you.

DR. GARCIA: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification for your vote if you wish to.

We'll start with Dr. Chen.

DR. A. CHEN: Andy Chen. I voted no. This is an efficacious drug, but I don't think it met the bar of safety.

DR. GARCIA: Thank you.

Dr. Freidlin?

DR. FREIDLIN: Boris Freidlin. I voted no for the following three reasons: first increase of toxicity; second, in the absence of OS improvement, modest PFS prolongation from continuous dose, and dose verse fixed administration is a questionable clinical benefit; and third, potential mortality detriment in the DUO trial, supported by experience with other PI3K inhibitors.

DR. GARCIA: Thank you.

Dr. Lieu?

DR. LIEU: This is Chris Lieu. I voted no. I thought this data was extremely difficult to interpret, but I'm in agreement with what's already been said. In the end, I do have concerns about this class of medication, and if we're not clearly improving overall survival in our patients but we're increasing toxicity and treatment-associated death, I'm not sure that we're truly helping patients. Thank you.

DR. GARCIA: Thank you.

Dr. Harrington?

DR. HARRINGTON: Dave Harrington. I voted no. Most of my reasons coincide exactly with Dr. Freidlin's and others. The other thing that I might add here is that as the FDA has pointed out, it's incumbent upon the sponsor to establish that there was a favorable risk-benefit profile, and I think given the current context, the data about this class, and extended follow up on this study, I don't think they've established that.

DR. GARCIA: Thank you.

Mr. Mitchell: Yes. This is really challenging. In large measure, because of the design of the trial, I think the sponsor hasn't shown substantial evidence that the drug is safe, and it may actually cause extreme harm, and even death in patients. The safety data from the other drugs in this class also informed my vote.

DR. GARCIA: Thank you, Mr. Mitchell.

Jorge Garcia. I voted no. I think I've stated earlier, I think this agent may work for some patients, may delay progression, but ultimately, as Dr. Harrington mentioned earlier,

these data do not support that this agent does prolong life, and on the contrary, appears to lead to excess toxicity for some.

Dr. Nieva?

DR. NIEVA: George Nieva. I voted yes. I think the drug reduces the burden of CLL in many patients. I do want to compliment the FDA and OCE for all the work they've done to bring to light the potential toxicity of this agent. They've done a great job issuing warnings on its use.

Some physicians and patients will determine that the data is insufficient to justify use of the drug; others will think it's the right drug for the right situation. Ultimately, I trust the decision making of physicians and patients to make informed decisions, and would like to see this drug available. Thank you.

DR. GARCIA: Thank you.

Ms. Nadeem-Baker?

(No response.)

DR. GARCIA: Ms. Nadeem-Baker?

MS. NADEEM-BAKER: Yes. I voted yes for

many of the same reasons as Dr. Nieva. This does work very well to bring down disease burden for patients who have already been on other therapies. The FDA is doing a great job, and I appreciate the importance of monitoring available drugs for toxicities, but for patients who have exhausted other treatments out there, this is needed in the arsenal of drugs for CLL patients, and now CLL patients are living longer thanks to other drugs, and they will need to be on treatment for decades. So this is why I voted yes.

DR. GARCIA: Thank you.

Dr. Sekeres?

DR. SEKERES: Hi. This is Mikkael Sekeres, and I voted no. I think that with this drug and this class of drugs, we are playing with fire. This drug had modest activity with significant toxicity, as did other members of this class, and was compared to a drug that we would no longer use in this setting. This drug itself, we would no longer use in this setting as patients receive other drugs such as BTK inhibitors and bcl-2

inhibitors, for which they would have been disqualified from the study. So we're left with a drug that has substantial toxicities and questionable indication today.

DR. GARCIA: Thank you.

Dr. Advani?

(No response.)

DR. GARCIA: Dr. Advani?

DR. ADVANI: Yes. Can you hear me now?

DR. GARCIA: Yes.

DR. ADVANI: Sorry about that.

I voted yes, mainly because I am not sure that the data was completely -- because of the study design, and everything, and the crossover, whether the overall survival detriment is as robust in this trial as made out to be. I do think this is an unmet need in this patient population. I acknowledge it's a class effect, and I really commend the FDA and applaud them for actually pointing this out to the broader community, and I hope that they will have the sponsor keep vigil on this trial, and maybe provide another follow-up a

year or two years down the line. And if this trend continues and becomes a stronger signal, we can revisit this question. But for now I wasn't sure that the data were completely compelling to vote no.

DR. GARCIA: Thank you.

Dr. Madan?

DR. MADAN: Yes. This is Ravi Madan. I voted yes. I think the task for the ODAC today was especially complicated. The use of a crossover design is very common in oncology and often seen as something advantageous to patients, as well as a accrual, and crossover is often a functional consequence of doing a study in the more indolent cancer, but in this case, the crossover design and also the asymmetric treatment exposure creates a very convoluted picture.

The true survival benefit of the investigative agent here may be obscured, and as the FDA suggested, a safety signal may also be somewhat obscured. But the FDA did not dispute the clinical efficacy of this therapy. I think as the

discussion today highlights, to a large degree, the available data can only partially inform opinions on the matter of safety, especially when progression may be associated with safety events in late-stage patients.

I've no doubt that duvelisib has toxicity associated with prolonged use, but I also have no way of accurately putting that toxicity data into the broader context of the disease state as opposed to a relative and asymmetric comparison to the control arm within this trial. Furthermore, I believe shifting treatment landscape of the disease state, continued FDA approval, and the class effect potential are really beyond the scope of this particular question.

Thus, it is key to me that this question is asking about the potential benefit in late-stage disease after at least two other therapies. In that case, perhaps the toxicities are warranted, given the higher stakes in late-stage disease. In this case, we may have to rely on the expertise of the treating physicians in making the choice to use

this agent if it continues to be available. Thank you.

DR. GARCIA: Thank you, Ravi.

Dr. Crawford?

DR. CRAWFORD: This is Stephanie Crawford. I voted no. Duvelisib is a benefit to some patients, though it's difficult to quantify the overall survival. Safety signals regarding toxicities, treatment-emergent AEs, and deaths are inconclusive, but they strongly warrant further study and consideration. Some aspects of the adequacy of the DUO trial design are fuzzy. The enrolled population was not sufficiently representative, and continued study would be strongly encouraged. Thank you.

DR. GARCIA: Thank you, Dr. Crawford.

Clearly, I think we all wrestle with the same challenges as a committee, and that probably is reflected on the difference in the vote. For those who voted yes, clearly it became the inability with the clinical trial design to fully be able to demonstrate detrimental outcome in

survival. They all felt the need for this agent in a heavily pretreated patient population when there's clearly an unmet clinical need for those patients, and may be able to actually use this treatment as a bridge to whatever next those patients may be able to get. Those who voted yes also felt that this would be something that the MD and the patient themselves should be able to actually address rather than us and the committee.

But all of us who actually felt that the answer was no, I think that I can summarize that in three statements. I don't think the data presented support that this agent does prolong life. Although the agent does have some activity and benefit for some patients, there are significant concerns for long-term toxicities and death related to some.

We all felt that it's hard to ignore the class effect of all PI3-kinase inhibitors, and certainly that was part of, also, some voting members' decision, and really the inability to fully demonstrate survival detriment because of the

confounding effect, something that really put a lot of pressure on our voting perhaps. But also equally important is how active this agent really is now that we're using an absolutely different treatment paradigm in the management of these patients with BTK inhibitors and bcl-2 inhibitors up front, and clearly there is no clear data to suggest that this agent, at least prospectively as I said earlier, would have any true benefit for this patient population in the contemporary setting.

Before we adjourn, are they any last comments from the FDA?

DR. S. CHEN: Excuse me, Dr. Garcia. This is the designated federal officer, She-Chia Chen. Before we go there, I would like to invite Dr. Advani -- can you please confirm your vote for the record, please? Thank you.

(No response.)

DR. GARCIA: Dr. Advani, I think the team needs to reconfirm your vote.

Go ahead.

DR. ADVANI: I voted yes.

DR. S. CHEN: Thank you.

DR. GARCIA: Thank you.

Again, are there any final comments from the FDA?

DR. GORMLEY: Yes. This is Nicole Gormley. I'd like to thank the committee for your deliberations and discussion. We really value your input, so thank you very much.

Adjournment

DR. GARCIA: Thank you, Dr. Gormley.

I'd like to actually express my gratitude to the entire members of the public; the FDA; the applicant, Secura Bio, Inc., and the entire committee for a robust discussion. Clearly, it's not an easy decision sometimes to vote. I always believe that in these circumstances, we're not asked to regulate or to define regulatory pathways for agents, but rather to review the data that is presented, and for us to provide our clinical expertise, and I think that's probably elements of what you saw today.

So thank you all for an active participation and have a great weekend, and stay safe and healthy. Thank you all. We adjourn the meeting now.

(Whereupon, at 1:37 p.m., the meeting was adjourned.)