FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Virtual Meeting

Thursday, April 21, 2022

12:00 p.m. to 3:45 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

She-Chia Chen, PharmD

Division of Advisory Committee and

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Office of Executive Programs, CDER, FDA

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C O N T E N T S

P R O C E E D I N G S

(12:00 p.m.)

Call to Order

DR. GARCIA: Good afternoon 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 Chanapa Tantibanchachai. 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 April 21, 2022 meeting of the Oncology Drug Advisory Committee to order. Dr. She-Chia Chen is the designated federal officer for this meeting, and she will begin with introductions.

Introduction of Committee

DR. S. CHEN: Good afternoon. My name is She-Chia Chen. I am the designated federal officer for this meeting. When I call your name, please introduce yourself by saying your name and affiliation. We will first start with ODAC members.

Dr. Advani?

DR. ADVANI: Dr. Advani, Stanford.

DR. S. CHEN: Dr. Conaway?

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

DR. S. CHEN: Dr. Cristofanilli?

DR. CRISTOFANILLI: Yes. Dr. Massimo Cristofanilli, breast medical oncologist, Weill Cornell, New York.

DR. S. CHEN: Dr. Garcia?

DR. GARCIA: Jorge Garcia, chief, medical oncology, University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, Ohio.

DR. S. CHEN: Dr. Lieu?

DR. LIEU: Christopher Lieu, GI medical oncologist, University of Colorado.

DR. S. CHEN: Dr. Madan?

DR. MADAN: Hi. Ravi Madan, GU medical oncologist, National Cancer Institute.

DR. S. CHEN: Mr. Mitchell?

MR. MITCHELL: I'm David Mitchell. I'm the consumer representative to the ODAC, and I'm the founder of Patients for Affordable Drugs, and I'm a

patient in ongoing treatment for hematological malignancy, multiple myeloma.

DR. S. CHEN: Dr. Nieva?

DR. NIEVA: Jorge Nieva, section head, Solid Tumors, University of Southern California, Norris Comprehensive Cancer Center.

DR. S. CHEN: And Dr. Sung?

(No response.)

DR. S. CHEN: Dr. Sung, I think you might be muted.

(No response.)

DR. S. CHEN: We'll go back to Dr. Sung later.

Next are our temporary voting members.

Dr. Au?

DR. AU: I'm Jessie Au. I'm founding director of Institute of Quantitative Systems Pharmacology, Carlsbad, California.

DR. S. CHEN: Dr. Chen?

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

DR. S. CHEN: Dr. Coffey?

DR. COFFEY: Chris Coffey. I'm a professor of biostatistics at the University of Iowa.

DR. S. CHEN: Dr. Diehl?

DR. DIEHL: Lou Diehl, hematologic malignancies, Duke University.

DR. S. CHEN: I'm going to go back to the ODAC member.

Dr. Sung, please unmute yourself, introduce yourself, and say your affiliation, please.

(No response.)

DR. S. CHEN: You're still muted, Dr. Sung. Can you give a shot?

(No response.)

DR. S. CHEN: Okay. We'll come back later.

I'll continue with temporary voting members.

Dr. Dunleavy?

DR. DUNLEAVY: I'm Kieron Dunleavy. I'm the director of hematology at Lombardi Cancer Center at Georgetown University in Washington, DC.

DR. S. CHEN: Dr. Kraft?

DR. KRAFT: Walter Kraft. I'm an internist and clinical pharmacologist at Thomas Jefferson

University in Philadelphia.

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

MS. NADEEM-BAKER: I am a CLL patient, and I am the patient representative on this panel.

DR. S. CHEN: And Dr. Thanarajasingam?

DR. THANARAJASINGAM: Dr. Thanarajasingam. I'm a lymphoma hematologist and a health outcomes researcher at the Mayo Clinic in Rochester, Minnesota.

DR. S. CHEN: Next are the industry representatives to the committee.

Dr. Cheng?

DR. CHENG: Hi. I'm Jonathan Cheng. I'm the industry rep. I'm a medical oncologist, and I'm with Bristol-Myers Squibb.

DR. S. CHEN: Last are FDA participants.

Dr. Pazdur?

DR. PAZDUR: Richard Pazdur, director, Oncology Center of Excellence, FDA.

DR. S. CHEN: Dr. Theoret?

DR. THEORET: Hi. Dr. Marc Theoret, deputy center director, Oncology Center of Excellence, FDA.

DR. S. CHEN: Dr. Gormley?

DR. GORMLEY: Hi. I'm a hematologist and the division director of the Division of Hematologic Malignancies II, FDA.

DR. S. CHEN: Dr. Richardson?

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

DR. S. CHEN: Dr. Kasamon?

DR. KASAMON: Hi. Yvette Kasamon, clinical team, Division of Hematologic Malignancies II, FDA.

DR. S. CHEN: Dr. Gwise?

DR. GWISE: Hello. I'm Thomas Gwise. I'm the director of the Division of Biometrics IX at FDA.

DR. S. CHEN: And Dr. Booth?

DR. BOOTH: Good afternoon. My name is Brian Booth. I'm the director of the Division of Cancer Pharmacology I in the Office of Clinical Pharmacology at the FDA.

DR. S. CHEN: Okay. I'm going to go back to Dr. Sung again.

Dr. Sung, please unmute yourself. Again,

introduce your name and say your affiliation. Thank you.

(No response.)

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

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that 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. S. 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 discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as

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

Today's agenda involves discussion of the appropriate approach for phosphatidylinositol 3-kinase inhibitors currently under development in patients with hematologic malignancies and whether randomized data should be required to support a demonstration of substantial evidence of the effectiveness and that the drug is safe for its intended use in the proposed population.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

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

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

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

by the committee's discussion. Thank you.

DR. GARCIA: We will proceed with the FDA introductory comments from Dr. Nicole Gormley.

Dr. Gormley?

FDA Introductory Comments – Nicole Gormley

DR. GORMLEY: Thank you.

Good afternoon. I'm Nicole Gormley, a hematologist in the Division of Hematologic Malignancies II at the FDA. I will provide a brief introduction to the PI3-kinase inhibitors and the reasons for discussing this drug class at an advisory committee meeting.

This committee meeting is not a typical ODAC where we would discuss the risk-benefit profile of a specific product, but instead we will discuss the class of PI3-kinase inhibitors as a whole, the unique toxicities they present, and the best development approach for future drugs in this class.

I'd like to start by providing a brief overview of the drugs in this class and their mechanisms of action. Overactivation of the PI3-kinase pathway is common in malignancy.

Activation of the PI3-kinase pathway can occur via several mechanisms, including mutations of the PI3KCA gene or mutations of downstream effector proteins.

Constitutive activation of the PI3-kinase pathway is common in hematologic malignancies. The PI3-kinase family of enzymes is grouped into three classes. Class 1A and 1B PI3 kinases activate or inhibit downstream proteins which affect cell growth, apoptosis, cell cycle regulation, glucose metabolism, and DNA repair.

The PI3-kinase inhibitors are targeted immunomodulatory drugs and inhibit different isoforms. The PI3-kinase inhibitors, which have been developed for hematologic malignancies, are listed here. All of the PI3-kinase inhibitors approved for hematologic malignancies inhibit the delta isoform. While idelalisib and umbralisib are selected delta inhibitors, copanlisib inhibits both delta and alpha isoforms, and duvelisib inhibits both delta and gamma. Umbralisib also inhibits casein kinase CK1 epsilon.

Of note, alpelisib is the only other

FDA-approved PI3-kinase inhibitor. It is approved for the treatment of PIK3CA mutated advanced or metastatic breast cancer and for the treatment of patients with severe manifestations of PIK3CA-related overgrowth spectrum. It is an alpha inhibitor and is not within the scope of the meeting today.

The PI3-kinase inhibitors' distinct mechanisms of action result in a differentiated safety profile depending on the isoform targeted. The delta and gamma isoforms are preferentially expressed on leukocytes, resulting in infections and immune-mediated toxicities.

The infections may occur, in part, because of treatment-related cytopenias, but also because of the modulation of the immune system by the PI3-kinase inhibitor. Infections include pneumonia, opportunistic infections like PCP and CMV reactivation.

With regards to the immune-mediated toxicities, the delta isoform is important for T regulatory cell function. It is thought that the decreased T regulatory cell activity and increased

CD8 cytotoxicity damages normal tissue, leading to the immune-mediated toxicities associated with these products. Hepatitis, pneumonitis, colitis, and rash have been observed. Younger patients and those less heavily pretreated with more robust immune systems may be at greater risk for these immune-mediated. toxicities.

The alpha isoform is ubiquitously expressed and is essential to cellular growth and metabolism, and glucose homeostasis. Result in toxicities from alpha inhibition include hyperglycemia and hypertension.

To highlight this further, I have included the common toxicities observed with the approved PI3-kinase inhibitors. Of note, there have been high rates of severe grade 3 or higher adverse events, high rates of serious adverse events, and significant discontinuations and dose reductions due to adverse events. The AEs observed include high rates of infection and immune-mediated toxicity. Copanlisib, the only inhibitor in hematologic malignancies that also inhibits the alpha isoform, has hyperglycemia

and hypertension-related toxicity.

This slide lists the labeling and other risk mitigation strategies used to communicate the risks associated with these products. Idelalisib and duvelisib have boxed warnings and communication REMS. The warnings and precautions for each of the products are listed.

The first PI3-kinase inhibitor approved in the U.S. was idelalisib in 2014. What is notable is that other than in CLL, where the initial approvals were based on randomized trials, the initial approvals for other indolent lymphomas -- follicular lymphoma, marginal zone lymphoma -- were based on single-arm trials and were granted accelerated approval.

Also of note, in December 2021, the sponsor for duvelisib, in consultation with the FDA, decided to voluntarily withdraw the FL indication, and in February 2022, the sponsor of idelalisib decided to voluntarily withdraw the FL and SLL indications for that product. And most recently, last week, the sponsor for umbralisib announced that they will

withdraw the FL and MZL indications. These withdrawals will be discussed further momentarily.

There are two approval pathways available in the U.S., regular approval and accelerated approval. Accelerated approval is available for drugs or biologics that are intended to treat a serious or life-threatening illness. The product should provide a meaningful therapeutic benefit over available therapy, and approval is based on an endpoint reasonably likely to predict clinical benefit or an intermediate endpoint. For products granted accelerated approval, there is often a requirement to conduct post-approval trials to verify the anticipated clinical benefit.

I'd like to briefly review the evidentiary criteria for approval. It is important to note that drugs granted accelerated approval or regular approval must meet the same statutory requirements for safety and effectiveness.

For safety, there must be sufficient information to determine that the drug is safe for use under the conditions prescribed, recommended, or

suggested in labeling. For effectiveness, there must be substantial evidence of effectiveness that allows for the conclusion that the drug will have the effect it purports or is represented to have under the conditions of use prescribed in labeling.

This slide outlines the FDA-approved treatment for CLL and indolent non-Hodgkin lymphoma. These products are often used together as part of combination therapy and may be used for retreatment at relapse. The approved classes include chemoimmunotherapies; cd20 monoclonal antibodies; BTK; BCL-2; and EZH2 inhibitors; and CAR T therapy.

There are several central issues that we will discuss further as it relates to the PI3-kinase inhibitors; specifically, a potential detriment in overall survival in multiple randomized trials; toxicity and tolerability of the PI3-kinase inhibitors; dosing considerations and an adequate dose optimization of several of the products to date; and the limitations of single-arm trials.

There have been several randomized-controlled trials evaluating a PI3-kinase inhibitor in

combination with immunotherapy or chemoimmunotherapy in patients with CLL or indolent non-Hodgkin lymphoma that have shown worse overall survival compared to the control arm.

Notably, the overall survival information from these trials is early and represents a low number of events; nevertheless, while the trials show a favorable impact on efficacy endpoints, just as progression-free survival or overall response rate, there have been higher rates of death, and the overall survival results are concerning.

It is also important to consider the patient population, those with CLL and indolent non-Hodgkin lymphoma. These diseases have a long natural history, and progression isn't necessarily an indication for treatment. While these are serious and life-threatening diseases and there is a need for continued development of products to treat relapsed or refractory disease, there are multiple therapeutics with established efficacy and safety.

While the PI3-kinase inhibitors have a unique toxicity profile and several trials have demonstrated

concerning overall survival results, some of these findings may be related to poor dose optimization. The optimal dose that maximizes efficacy and minimizes safety may not have been identified.

Across their class, there's been limited dose exploration. Many doses were determined using a maximum tolerated dose, or MTD, approach, with limited exploration of lower dose levels. For each of the approved PI3-kinase inhibitors, there are exposure-response relationships for safety, but exposure-response relationships for efficacy have not been consistently observed. High rates of discontinuation, interruption, and modification also suggest the approved doses may be poorly tolerated.

There have been voluntary withdrawal of approval of three PI3-kinase inhibitor indications to date: idelalisib, duvelisib, umbralisib. Idelalisib for relapsed/refractory FL or SLL was granted accelerated approval in 2014 based on a single-arm trial. At the time, three accelerated approval postmarketing requirements were issued to verify the clinical benefit.

The first PMR was a dose optimization study for chronic administration. The second PMR required submission of the final report and data showing safety and efficacy from study 0124, a phase 3, 2-arm, randomized placebo-controlled trial of idelalisib in combination with rituximab in patients with previously treated iNHL. And finally, the third PMR required submission of the results from Study 0125, a phase 3 randomized, placebo-controlled trial of idelalisib in combination with bendamustine and rituximab in patients with previously treated iNHL.

In 2016, the FDA was notified that three randomized control trials were terminated due to increased death in the idelalisib arm. These terminated trials included the 0124 and 0125 accelerated approval confirmatory trial. The third terminated trial was evaluating idelalisib in combination with bendamustine and rituximab in patients with treatment naïve CLL.

Several regulatory actions were taken by the FDA as a result of these findings. A limitation of

use was added to the label that idelalisib is not indicated for first-line treatment and is not indicated in combination with bendamustine and rituximab in follicular lymphoma.

There were updates to the boxed warning and warnings and precautions. A new PMR was issued to conduct a trial to establish the safe and effective dose of idelalisib in patients with relapsed/refractory FL who have no other therapeutic options. The PMR was to be supported by Study 1580.

In February 2022, citing challenges in enrollment to the confirmatory trial and inability to provide evidence to verify the clinical benefits of idelalisib in patients with FL and SLL, the sponsor in consultation with the FDA decided to voluntarily withdraw the FL/SLL indication from the U.S. market.

The second voluntary withdrawal was for duvelisib. Duvelisib for relapsed/refractory FL was granted accelerated approval in 2018 based on a single-arm trial. At that time, one accelerated approval postmarketing requirement was issued to verify the clinical benefit. The planned trial to

support this was going to be the DUETTO trial, the phase 3 randomized trial of duvelisib plus rituximab compared with rituximab alone or rituximab in combination with CDP. The trial was never initiated due to feasibility issues and a changing treatment landscape. Because of the inability to provide evidence to verify the clinical benefit of duvelisib in patients with FL, the sponsor in consultation with the FDA decided to voluntarily withdraw the indication from the U.S. in December of 2021.

On April 15, 2022, the umbralisib and ublituximab applications for the U2 combination regimen were voluntarily withdrawn. This was due to updated overall survival data from the unity UNITY-CLL trial which showed an increase in overall survival imbalance in favor of the control arm. At the same time, the sponsor also announced the voluntary withdrawal of the existing umbralisib indication of relapsed/refractory FL and MZL under accelerated approval.

The withdrawn indications were under accelerated approval in which the approvals were

based on single-arm trials. With the PI3-kinase inhibitors, we have seen several instances in which the confirmatory trial with randomized data identified concerning overall survival results and concerning toxicity. It is worth underscoring at this point some of the limitations of single-arm trials.

In single-arm trials, the safety findings are challenging to interpret. Without a comparator, it can be challenging to attribute adverse events observed to the drug or to the underlying disease. The efficacy can also be challenging to interpret. The responses observed may not translate into true clinical benefit.

Comparisons due to historical populations or cross-trial comparisons are fraught with limitations. When evaluating single-arm trials for accelerated approval, there is a requirement that the therapy provide a clinically meaningful advantage over available therapy. Given the different temporal conduct of trials, differences in the patient population and other changes to standards of care,

the comparative assessment can be challenging.

Finally, because of the aforementioned limitations of cross-trial and historical comparisons, to avoid these and other biases, time-to-event endpoints such as progression-free survival and overall survival cannot be accurately assessed or interpreted in single-arm trials. Therefore, in a single-arm trial, it is hard to balance the observed efficacy with toxicity to appreciate the true benefit-risk of the drug in the intended patient population.

The inability to assess overall survival in single-arm trials is important because overall survival is an objective measure of clinical benefit and is both a safety and an efficacy endpoint. Overall survival incorporates the impact of toxicity and is useful in assessing both short-term and long-term impacts of therapy.

We would like for the committee to please discuss the observed toxicity of the PI3-kinase inhibitor class and whether randomized data are warranted with an assessment of OS to support the

evaluation of benefit-risk in patients with hematologic malignancies.

The voting question is, given the observed toxicities with this class, previous randomized trials with the potential detriment in OS, and a narrow range between effective and toxic doses, should future approvals of PI3-kinase inhibitors be supported by randomized data?

Thank you for your attention. Dr. Richardson will discuss these issues in further detail?

DR. GARCIA: Thank you, Dr. Gormley.

We will now proceed with the FDA presentation with Dr. Nicholas Richardson.

Dr. Richardson?

FDA Presentation – Nicholas Richardson

DR. RICHARDSON: Good afternoon. I'm Nicholas Richardson, a pediatric hematologist/oncologist in the Division of Hematologic Malignancies II at the FDA. I will be presenting the FDA's discussion on the PI3K inhibitors in hematologic malignancies.

As mentioned by Dr. Gormley, this ODAC

meeting is not a typical product-specific ODAC. We are here to discuss the class of PI3K inhibitors as a whole, the unique toxicities they present, and the best drug development approach for future PI3K inhibitors that are developed in patients with hematologic malignancies.

To support a class discussion, I will highlight relevant data for each of the approved PI3K inhibitors and hematologic malignancies that are shown on the slide. This will be followed by a class-wide discussion. The central issues we would like to focus on today are multiple randomized trials showing a potential detriment in overall survival; toxicity of the PI3K inhibitor class; dosing considerations and dose optimizations; and trial design considerations regarding limitations of single-arm trials.

The members of the FDA review team are listed here. My presentation represents their collective input. I would like to start with a brief overview of the timeline for the approved PI3K inhibitors in hematologic malignancies and relevant milestones.

The first PI3K inhibitor approved in the U.S. was idelalisib in 2014 for patients with chronic lymphocytic leukemia, follicular lymphoma, and small lymphocytic lymphoma. The FL and SLL indications were granted accelerated approval based on a single-arm trial.

Subsequently, in March 2016, the FDA was notified regarding three randomized trials with idelalisib showing early signs of worse overall survival. This prompted an FDA safety alert and an update to the idelalisib label with updated safety information and limitations of use.

In February of this year, the FL and SLL indications under accelerated approval were voluntarily withdrawn due to the inability to provide evidence to verify clinical benefit for idelalisib in patients with FL or SLL.

The second PI3K inhibitor approved was copanlisib in 2017. Copanlisib was granted accelerated approval in patients with relapsed follicular lymphoma based on a single-arm trial. In May of 2021, a supplemental new drug application for

copanlisib in patients with indolent non-Hodgkin lymphoma was submitted based on the randomized CHRONOS-3 trial. The application was subsequently withdrawn in December of 2021 to allow for additional analyses of data from ongoing trials.

The third PI3K inhibitor approved was duvelisib in 2018. Duvelisib was approved for patients with CLL or SLL and follicular lymphoma. The FL indication was an accelerated approval based on a single-arm trial. In December 2021, the follicular lymphoma indication was voluntarily withdrawn due to the inability to provide evidence to verify clinical benefit for duvelisib in patients with follicular lymphoma.

Lastly, umbralisib was granted accelerated approval for follicular lymphoma and marginal zone lymphoma in February 2021 based on a single-arm trial. A subsequent supplemental new drug application was submitted in May 2021 for patients with CLL and SLL based on the randomized UNITY-CLL trial. Based on ongoing analyses and concerns with the UNITY-CLL trial, an FDA safety alert was issued

in February 2022 for a possible increased risk of death in those treated with umbralisib.

Last week on April 15th, the application based on the UNITY-CLL trial was withdrawn from the FDA. In addition, the existing FL and MZL indications for umbralisib, currently under accelerated approval, are being voluntarily withdrawn from the U.S. market.

Now we will transition to discussing the relevant data for the approved PI3K inhibitors. We will start with idelalisib, a PI3K delta inhibitor. The issues we will highlight our decrements in overall survival in several randomized trials, PI3K associated toxicity, and dosing considerations.

Idelalisib was granted regular approval for patients with relapsed CLL in combination with rituximab in patients for whom rituximab alone would be considered appropriate. The approval was based on the 0116 study, a randomized placebo-controlled trial that demonstrated a statistically significant benefit in progression-free survival in those treated with idelalisib plus rituximab, with an approximate

13-month Improvement in PFS with an adjusted hazard ratio of the 0.15. At the time of approval, the overall survival information was early with a total of 19 overall survival events, or 9 percent, with an estimated OS hazard ratio of 0.37, favoring the idelalisib arm.

Idelalisib as monotherapy was also granted accelerated approval for patients with relapsed follicular lymphoma or small lymphocytic lymphoma after at least two prior systemic therapies. This was based on an overall response rate of 54 percent in follicular lymphoma and 58 percent in small lymphocytic lymphoma with associated durability from a single-arm trial.

Based on the trial supporting the initial approval of idelalisib, a notable toxicity profile was observed. To mitigate risk, several measures were included as part of the initial approval: a boxed warning used to highlight adverse reactions so serious in proportion to the potential benefit from the drug that it is essential that it be considered in assessing the risk and benefits of using the drug.

The initial approval of idelalisib included a boxed warning for hepatotoxicity, diarrhea or colitis, pneumonitis, and intestinal perforation. Additionally, the toxicities rash, neutropenia, and anaphylaxis were included as warnings and precautions.

A risk evaluation and mitigation strategy, or REMS, was included with the initial approval of idelalisib. A REMS is a safety program used to ensure a drug is safe and effective for its intended use and that its benefits outweigh its risks.

Along with risk mitigation, a number of postmarketing requirements were issued for idelalisib. There was a postmarketing requirement issued to conduct a trial to optimize the dose of idelalisib in patients with follicular lymphoma or small lymphocytic lymphoma. Additionally, two postmarketing requirements were issued to verify the clinical benefit of idelalisib in patients with indolent non-Hodgkin lymphoma based on two ongoing randomized trials. A total of four additional postmarketing requirements for safety were issued.

These included characterization of the risk of pneumonitis and to characterize long-term safety across ongoing trials.

In March of 2016, the FDA was notified of three randomized trials evaluating idelalisib in combination with immunotherapy or chemoimmunotherapy that were terminated due to increased deaths and severe toxicity in idelalisib arms. These trials are the 0123 trial in patients with untreated CLL and the 0124 and 0125 trials in patients with previously treated indolent non-Hodgkin lymphoma. Each of the trials was a randomized, double-blind, placebo-controlled trial. The respective treatment arms are shown in the table.

This table shows the interim overall survival results for the three randomized trials. In each trial, there were more deaths in the idelalisib arm compared to the control arm. Despite a limited number of overall survival events, the estimated hazard ratio for these trials showed the potential for an increased risk of death and harm to patients. The reasons for death in the three randomized trials

indicate a higher rate of death due to adverse events in the idelalisib arm. The primary adverse events leading to death were infections, as shown in the table.

This graph shows the safety results from the three randomized trials. For grade 3 or greater toxicity, serious adverse events and discontinuation, dose reduction, or dose interruption due to an adverse event, the rates were notably higher in the idelalisib arms, as indicated by the blue bars in the graph. Even with treatment modifications due to adverse events, the increased rates of grade 3 or greater toxicity and serious adverse events indicate overall safety concerns with idelalisib in the evaluated populations and uncertainty regarding the idelalisib dosing regimen.

The safety results from the three randomized trials demonstrate that the PI3K associated toxicities of grade 3 or greater infection -- neutropenia, diarrhea or colitis, increased ALT or AST, rash, and any grade pneumonitis -- are driving the differences in safety

between the treatment arms. Shown in the table, the incidence of any grade pneumonitis or grade 3 or greater PI3K associated toxicities, except neutropenia, are 2 to 3 times higher compared to the control arm.

The data from the three idelalisib randomized trials led to an FDA safety alert regarding higher deaths and severe toxicity. A Dear Healthcare Provider Letter was also issued. Additional risk mitigation measures were implemented. The boxed warning for idelalisib and the REMS were updated to include the risk of fatal or serious infections.

The safety data from the three randomized trials was included in labeling, and most importantly, the randomized data informed limitations of use for idelalisib. The limitations of use include the frontline treatment of any patient and that idelalisib is not indicated or recommended in combination with rituximab or in combination with bendamustine and rituximab in patients with follicular lymphoma.

The three terminated idelalisib trials

included the 0124 and 0125 accelerated approval confirmatory trials for idelalisib in indolent non-Hodgkin lymphoma; therefore, a new accelerated approval postmarketing requirement was issued. The new postmarketing requirement was to identify a safe and effective dosing regimen in patients with follicular lymphoma who have exhausted known treatment options.

Study 1580 was an ongoing study evaluating different dose levels and different regimens of idelalisib in patients with follicular lymphoma. The 1580 study encountered enrollment challenges. Ultimately, because of the inability to provide evidence to verify the clinical benefit of idelalisib in patients with follicular lymphoma and small lymphocytic lymphoma, as required per the accelerated approval regulations, the FL and SLL indications for idelalisib were voluntarily withdrawn in February of this year.

Given the toxicity concerns and the impact on overall survival in randomized trials, it is important to look at the dose exploration in the

selected dose of idelalisib. The approved dose for idelalisib is 150 milligrams BID or twice daily. As monotherapy, the maximum tolerated dose for idelalisib was not reached.

Exposure-response for efficacy plateaued at 150 milligrams. There was an exposure-response relationship for safety with higher exposures associated with increased toxicity, and this was coupled with high rates of treatment modifications due to toxicity.

In combination, idelalisib 150 milligrams BID was also selected. There was limited dose exploration in combination and, again, there was no exposure-response relationship for efficacy, but there was an exposure-response relationship for safety. Ultimately, lower doses of idelalisib as monotherapy or in combination may have warranted further exploration.

The second PI3K inhibitor is copanlisib, an alpha and delta PI3K inhibitor. The issues we will highlight our overall survival concerns in the CHRONOS-3 trial, PI3K associated toxicity, and

considerations for the selected dose. In 2017, copanlisib was granted accelerated approval for patients with relapsed follicular lymphoma who have received at least two prior systemic therapies. The approval was based on the CHRONOS-1 trial, a single-arm trial that showed an overall response rate of 59 percent with associated durability.

A pooled safety database of 244 patients with non-Hodgkin lymphoma demonstrated a notable toxicity profile. There was a high rate of grade 3 or greater adverse events at 85 percent, serious adverse events at 51 percent, and high rates of treatment modification due to toxicity.

Since copanlisib inhibits the PI3K alpha isoform, it is associated with hyperglycemia and hypertension. The incidence of grade 3 or greater hyperglycemia was 34 percent. Grade 3 or greater hyperglycemia represents a blood glucose greater than 250 to over 500 milligrams per deciliter with hospitalization indicated. For hypertension, the incidence of grade 3 or greater hypertension was 29 percent. Grade 3 or greater hypertension

indicates the need for medical intervention.

To mitigate risk, the toxicities of infection, hyperglycemia, hypertension, pneumonitis, neutropenia, and rash were included as warnings and precautions because they represented adverse reactions or safety hazards that are serious, clinically significant, and have implications for prescribing decisions or for patient management.

In addition, a number of postmarketing requirements were issued for copanlisib. For accelerated approval, a postmarketing requirement was issued to verify the clinical benefit of copanlisib in patients with non-Hodgkin lymphoma based on an ongoing randomized trial. A total of five additional postmarketing requirements for safety were issued as shown.

A supplemental new drug application for copanlisib was submitted in May 2021 for copanlisib in combination with rituximab for the treatment of patients with relapsed indolent non-Hodgkin lymphoma. The application was based on the CHRONOS-3 trial, a randomized placebo-controlled trial, evaluating

rituximab with or without copanlisib and a primary endpoint of progression-free survival. The population was patients with indolent non-Hodgkin lymphoma that included follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma, and Waldenstrom's macroglobulinemia. The majority of patients enrolled had follicular lymphoma and marginal zone lymphoma.

Importantly, the target population was those patients that did not require intensive therapy and were defined as either progression free or treatment free for 12 months or more following the last anti-CD20 based therapy, or considered unfit for chemotherapy due to comorbidities and progression free or treatment free for 6 months or more following the last anti-CD20 based therapy.

In the intent-to-treat population, the CHRONOS-3 trial showed a statistically significant benefit in progression-free survival in those treated with copanlisib plus rituximab with an approximately 8-month improvement in PFS, with an adjusted hazard ratio of 0.52.

Here are the interim overall survival data for the CHRONOS-3 trial. The Kaplan-Meier curve on the left is for the intent-to-treat population in indolent non-Hodgkin lymphoma, and the curve on the right is in patients with follicular lymphoma, which represented 60 percent of the trial population.

It is notable that the copanlisib arm shows worse overall survival compared to the control arm within approximately the first two years. This is followed by a crossing of the curves yielding the estimated hazard ratio of less than 1. However, this pattern indicates a concern for potential harm early in the treatment setting with copanlisib in patients with indolent non-Hodgkin lymphoma who are suitable for treatment with single-agent rituximab.

This table shows the reason for death in the CHRONOS-3 trial. The deaths due to adverse events were higher in the copanlisib arms and encompassed infections, respiratory, and cardiac causes. This graph shows the safety results from the CHRONOS-3 trial. For grade 3 or greater toxicity, serious adverse events and discontinuation, dose reduction,

or dose interruption due to an adverse event, the rates were notably higher in the copanlisib arm, as indicated by the blue bars in the graph.

Safety results from the CHRONOS-3 trial demonstrate that the PI3K associated toxicities of grade 3 or greater hyperglycemia, hypertension, infection, neutropenia, diarrhea or colitis, and any grade pneumonitis are driving the differences in safety between the treatment arms. Shown and indicated in the table, the incidence of any grade pneumonitis, or grade 3 or greater PI3K associated toxicities, except increased ALT or AST, are substantially higher compared to the control arm.

Based on ongoing analysis of the CHRONOS-3 trial, the supplemental new drug application for copanlisib in combination with rituximab, in patients with indolent non-Hodgkin lymphoma, was voluntarily withdrawn from the FDA in December 2021.

Turning to the selected dose of copanlisib, there are some important considerations. The approved dose of copanlisib is 60 milligrams IV, administered weekly for 3 weeks in a 28-day treatment

cycle. Notably, the 60-milligram dose was identified as a maximum tolerated dose and there was limited dose finding in patients with hematologic malignancies.

The PK and PD data suggested comparable efficacy at a 45-milligram dose and 60-milligram dose. There were high rates of treatment modification due to toxicity at the 60-milligram dose level. Further, the 60-milligram dose was selected to be used in combination, and there was no dose exploration for copanlisib in combination.

The third PI3K inhibitor is duvelisib, a delta and gamma PI3K inhibitor. The issues we will highlight our concerning overall survival, PI3K associated toxicity, and dosing considerations.

Duvelisib was granted regular approval for patients with relapsed or refractory CLL or SLL after at least two prior therapies in September 2018. The approval was based on the DUO study, a randomized open-label trial that demonstrated a statistically significant benefit in progression-free survival in those treated with duvelisib. The PFS result in the

ITT population are shown in the table.

The DUO trial enrolled patients who had received at least one prior therapy, but because of safety concerns, the indication was restricted to patients who had received at least two prior therapies. At the time of approval, the overall survival hazard ratio in those patients who had received at least two prior therapies was 0.82, favoring duvelisib.

Duvelisib was also granted accelerated approval for patients with relapsed or refractory follicular lymphoma after at least two prior systemic therapies, based on an overall response rate of 42 percent with associated durability from the single-arm DYNAMO trial.

The pooled safety database of 442 patients with non-Hodgkin lymphoma demonstrated a notable toxicity profile with duvelisib. There were high rates of grade 3 or greater toxicity at 84 percent, serious adverse events at 65 percent, and high rates of treatment modifications due to adverse events. The table on the right shows the grade 3 or greater

PI3K associated toxicities and any grade pneumonitis for duvelisib, several of which included fatal and serious events.

This graph shows the safety results from the randomized DUO trial in patients with CLL and SLL for death due to adverse events; grade 3 or greater toxicity; serious adverse events and discontinuation; dose reduction; or dose interruption 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 demonstrates that the PI3K associated toxicity of grade 3 or greater infection, neutropenia, diarrhea or colitis, increased ALT or AST, rash, and any grade pneumonitis are driving the differences in safety between the treatment arms. Shown and indicated in the table, the incidence of any grade pneumonitis or 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.

To mitigate risk, several measures were

included as part of the initial approval for duvelisib. Similar to idelalisib, duvelisib included a boxed warning for infection, diarrhea or colitis, rash, and pneumonitis. Additionally, the toxicity of neutropenia and hepatotoxicity were included as warnings and precautions. A risk evaluation and mitigation strategy was included with the initial approval of duvelisib to ensure its safe and effective use and that its benefits outweigh its risks.

Along with risk mitigation, several postmarketing requirements were issued for duvelisib. For accelerated approval, a postmarketing requirement was issued to verify the clinical benefit of duvelisib in patients with relapsed or refractory follicular lymphoma. Additional postmarketing requirements were issued for safety that included characterization of long-term safety across ongoing trials and the final overall survival analysis of the DUO trial.

As mentioned, FDA required the final OS analysis of the DUO trial be submitted as a

postmarketing requirement. Here is the recent final OS analysis with a median OS follow-up of 63 months. The data for the final OS analysis is currently undergoing FDA review.

The sponsor was required to conduct a confirmatory trial to verify the clinical benefit of duvelisib in relapsed or refractory follicular lymphoma. The DUETTO trial, or randomized trial evaluating duvelisib in combination with rituximab, compared to investigators choice of rituximab or R-CVP in patients with follicular lymphoma, was intended to be the confirmatory trial for duvelisib.

The trial was never initiated due to feasibility issues and a changing treatment landscape. Because of the inability to provide evidence to verify the clinical benefit of duvelisib in patients with follicular lymphoma, as required per the accelerated approval regulation, the FL indication was voluntarily withdrawn in December 2021.

For duvelisib, the approved dose is 25 milligrams BID. In general, there was limited

dose exploration, and 75 milligrams was identified as the MTD. There was no exposure-response relationship for efficacy at 25 milligrams BID, and PD data showed near maximal suppression of the p-AKT biomarker at 25 milligrams. There were exposure-response relationships for toxicity between 8 milligrams and 75 milligrams, and the 25-milligram dose was associated with high rates of treatment modification due to adverse events.

Lastly, the fourth PI3K inhibitor is umbralisib, a delta PI3K inhibitor. Umbralisib was granted accelerated approval for patients with relapsed or refractory follicular lymphoma who have received at least three prior lines of systemic therapy, and for marginal zone lymphoma who have received at least one prior anti-CD20 base regimen. The approvals were based on the UTX-TGR-205 trial, a single-arm, multicohort trial that showed an overall response rate of 43 percent in follicular lymphoma and 49 percent in marginal zone lymphoma for the associated durability.

A subsequent supplemental new drug

application for umbralisib was submitted in May 2021 for patients with CLL and SLL, based on the UNITY-CLL trial, a randomized trial evaluating umbralisib in combination with ublituximab, the U2 regimen, versus obinutuxumab and chlorambucil in patients with CLL. Based on ongoing analyses and concerns with the UNITY-CLL trial, an FDA safety alert was issued in February 2022 for a possible increased risk of death in those treated umbralisib.

On April 15th, last week, the supplemental NDA for umbralisib and the BLA for ublituximab for the U2 combination regimen, for the treatment of patients with CLL or SLL, was voluntarily withdrawn from the FDA. This was due to updated overall survival data from the UNITY-CLL trial, which showed an increasing overall survival imbalance in favor of the control arm. At the same time, the sponsor announced the voluntary withdrawal of umbralisib from the U.S. market for the indications of relapsed or refractory follicular lymphoma and marginal zone lymphoma under accelerated approval.

With that, I'd like to turn to our discussion

of the PI3K class and the topics as shown: a potential detriment in overall survival across multiple randomized trials; the differentiated safety profile of this class and how it impacts tolerability; dosing concerns with the selected doses; and the paradigm of single-arm trials.

As a class, multiple randomized trials, as shown in the table, evaluating a PI3K inhibitor as monotherapy or in combination in patients with CLL or indolent non-Hodgkin lymphoma, have shown a decrement or concerning overall survival compared to the control arm. Notably, the overall survival information from these trials is early and represents a low number of events, however, we are observing the same pattern repeated across multiple randomized trials.

In addition, the trials show a favorable impact on efficacy endpoints such as progression-free survival or overall response rate, indicating that the overall survival concerns are a primary safety concern. This is reiterated by the fact that a higher rate of death due to adverse events was

observed in the PI3K inhibitor arms across these trials.

It is also important to consider two additional components, the population of patients and the comparator arms. The patients are those with CLL and indolent non-Hodgkin lymphoma. Diseases that have a long natural history, progression isn't necessarily an indication for treatment and patients have multiple effective treatment options with known efficacy and safety.

For the comparator arms, they represent single-agent CD20 monoclonal antibodies or chemoimmunotherapy regimens, each with a favorable and tolerable safety profile, setting up an optimal comparative background to assess toxicity of the investigative PI3K inhibitor arm and its effect on overall survival. PI3K inhibitors have substantial toxicities that can be fatal or serious. The toxicities observed are driven by PI3K associated toxicities related to the mechanism of action of these agents.

This table shows the incidence of PI3K

associated toxicities for the approved PI3K inhibitors in patients with hematologic malignancies when administered as monotherapy. The incidence of the respective grade 3 or greater toxicities are notable and reiterate the overall safety concerns with this drug class.

When looking at the overall safety results from the randomized trials evaluating PI3K inhibitors, each trial has shown higher rates of death due to adverse events, grade 3 or greater toxicity, serious adverse events, and treatment modifications. The differences in safety are driven by the PI3K associated toxicities.

Given the toxicity concerns with the PI3K inhibitor class, optimized dosing is warranted. The PI3K inhibitors exhibit a narrow range between an effective and toxic dose. Across the class, there has been limited dose exploration.

For each improved PI3K inhibitor, there are exposure-response relationships for safety, primarily for PI3K associated toxicities. Conversely, exposure-response relationships for efficacy have

generally not been observed. Despite the need to balance efficacy along with safety and tolerability, there has been insufficient dose exploration as monotherapy and in combination for these agents.

As noted, PI3K inhibitors have exposure-response relationships for safety, with higher exposure leading to increased risk for toxicity. These graphs show that with higher PI3K inhibitor exposure, there is an increased risk of diarrhea with idelalisib and umbralisib, as shown in the top left; an increased risk of infection and specifically pneumonia with duvelisib; and an increased risk of hepatotoxicity with duvelisib and umbralisib, as shown on the right. This is in the setting that generally no exposure-response relationships have been observed for efficacy.

Dose modification data from the approved PI3K inhibitors suggest tolerability concerns. Because of toxicity, a number of patients discontinue treatment or require dose reductions or interruptions. These graphs show the number of patients that receive each dose per cycle for idelalisib, duvelisib, and

copanlisib as monotherapy at the currently recommended doses. As shown, a number of patients require treatment modification early in the treatment course, and many end up discontinuing therapy. This reiterates the need for adequate dose exploration and identification of an optimal dose.

In addition, rigorous measurement of patient-reported side effects during dose finding or registrational trials allow for a better understanding of tolerability and toxicity. Information on patient-reported symptomatic adverse events were limited or not completed for the approved PI3K inhibitors.

The last issue we would like to highlight today is the paradigm of using single-arm trials to support an assessment of benefit-risk for PI3K inhibitors. Given the toxicity concerns noted, the prior issues discussed for the PI3K inhibitors highlight the limitations of single-arm trials. For most, without a comparator arm, it is challenging to characterize safety. The side effects observed could be due to the drug or to the underlying disease.

Additionally, within a single-arm trial, the follow-up is often relatively short and characterizing long-term safety is limited. Second, the assessment of efficacy is less robust because comparison to a historical control or across populations has known limitations. Further, response rate may not predict clinical benefit. And finally, time-to-event endpoint such as progression-free survival and overall survival cannot be accurately interpreted in single-arm trials. In a single-arm trial, it is hard to balance the observed efficacy with toxicity to appreciate the true benefit-risk of the drug in the intended population.

As noted, the PI3K inhibitor approvals for patients with indolent non-Hodgkin lymphoma were based on single-arm trials, and were accelerated approvals with a requirement to conduct a confirmatory trial to verify clinical benefit. The FL and SLL indications for idelalisib were voluntarily withdrawn in February of this year due to enrollment challenges in the ongoing confirmatory study. The FL indication for duvelisib was withdrawn

in December 2021, as a confirmatory study was never initiated due to feasibility concerns and a changing treatment landscape.

Last week, the umbralisib FL and MZL indications were voluntarily withdrawn based on concerns from a randomized trial in a relevant population. The withdrawals of the indications and the reasons for the withdrawals further highlight the limitations of the paradigm of using single-arm trials for development and potential registration of PI3K inhibitors.

On the last slide, we discuss the limitations of single-arm trials. We would like to take a moment and highlight the benefits of randomized trials.

Randomized trials are the preferred approach to evaluate a treatment and determine whether it provides clinical benefit. The act of randomization balances patient characteristics, both known and unknown factors, between the treatment groups, allowing attribution of any differences in the study outcomes to the treatment being evaluated. This is not possible with any other non-randomized design.

The act of randomization can also help reduce bias, including selection bias. Lastly, time-to-event endpoints such as progression-free survival and overall survival can be adequately assessed and interpreted in a randomized trial.

The findings in the randomized trials of the PI3K inhibitors highlight the importance of overall survival information. While overall survival is not always feasible as a primary endpoint such as in trials in CLL and indolent non-Hodgkin lymphoma, where progression-free survival is used as a primary endpoint due to the long natural history of the disease and multiple therapeutic options, overall survival is an endpoint that should be analyzed in all randomized trials.

The FDA requires overall survival information for any trial that uses progression-free survival as a primary endpoint. Overall survival is an objective measure of clinical benefit and is considered both an efficacy and a safety endpoint. An evaluation of toxicity is embedded in an assessment of overall survival, including the ability to assess short-term

and long-term toxicity. 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 evaluated as a safety endpoint.

As mentioned, time-to-event endpoints such as overall survival can only be accurately assessed and interpreted in a randomized trial. Finally, overall survival is an important metric in supporting a benefit-risk determination, especially in the setting of substantial toxicity.

To end my presentation today, I'd like to review the evidentiary criteria that must be provided by sponsors to support approval. For safety, there must be sufficient information to determine that the drug is safe for use under the conditions prescribed, recommended, or suggested in labeling. For effectiveness, there must be substantial evidence of effectiveness that allows for the conclusion that the drug will have the effect it purports or is represented to have under the conditions of use prescribed in labeling.

Ultimately, it is incumbent upon sponsors to provide evidence to the FDA to support that the drug is safe and effective in the intended population from an adequate and well-controlled trial or trials.

In conclusion, the PI3K inhibitor class has substantial toxicity primarily related to the mechanism of action of these agents. The toxicity concerns have translated into a potential detriment in overall survival in multiple randomized trials in patients with CLL or indolent non-Hodgkin lymphoma, which is unprecedented in oncology. The PI3K inhibitors have tolerability concerns with high rates of treatment modification due to toxicity. As a class, dose exploration and optimization has been insufficient, especially given the narrow range between effective and toxic doses.

Finally, there has been a reliance on single-arm trials in patients with indolent non-Hodgkin lymphoma, limiting the assessment of efficacy and safety and precluding evaluation of the impact on time-to-event endpoints such as overall survival. Therefore, experience with the PI3K

inhibitor class in patients with hematologic malignancies requires a re-examination of PI3K inhibitor development and the approach needed for sponsors to provide adequate evidence to determine safety and efficacy.

We would like the committee to discuss the following. Please discuss the observed toxicity of the PI3K inhibitor class and whether randomized data are warranted with an assessment of overall survival to support the evaluation of benefit-risk in patients with hematologic malignancies.

The voting question: given the observed toxicities with this class, previous randomized trials with a potential detriment in overall survival, and a narrow range between effective and toxic doses, should future approvals of PI3K inhibitors be supported by randomized data?

Thank you. This concludes my presentation.

DR. S. CHEN: This is DFO She-Chia Chen. At this time, I would like to invite Dr. Anthony Sung, an ODAC member, to please introduce yourself and say your affiliation into the record.

Dr. Sung? Thank you.

DR. SUNG: Hi. This is Anthony Sung. I'm an associate professor of medicine in the Division of Hematologic Malignancies and Cellular Therapy at Duke University. Sorry. I had stepped away for a moment during the original introduction period.

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

Now I will hand it over to Dr. Garcia.

Clarifying Questions to Presenters

DR. GARCIA: Thank you, Dr. Chen.

We will now take clarifying questions for the presenters, the FDA. Please use the raised-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.

Dr. Nieva?

DR. NIEVA: Thank you. This is Jorge Nieva from USC. My question is for Dr. Richardson, and it relates to the safety of these drugs over time.

It seems that the trial design for many of these studies was a treat-until-progression design. However, that is not the way that many indolent lymphomas are treated, where the patients are treated to best response rather than until progression. I guess my question is, are there data on duration of therapy and toxicity? And I guess the follow-up question to that is, are there any guidances from the FDA to sponsors as to whether or not there was a need for a treat-to-progression design? Thank you.

DR. GORMLEY: This is Nicole Gormley. This question was directed to Dr. Richardson, and I'll have him start, and then I will add on.

DR. RICHARDSON: Hi. This is Nicholas Richardson, FDA. Thank you for that question. I'll try to address them one at a time.

One, you had mentioned timing. If you look at the safety of these agents when they are administered as monotherapy, the exposure in the pooled safety database that was submitted as part of the initial evaluation of safety that supported the approval of these agents, we saw that the median exposure was typically 6 months or less. Specifically for idelalisib, it was a median of 6 months; copanlisib was a meeting of 4.3 months; umbralisib was a median of 5.9 months; and duvelisib was actually a little bit longer with a median of 9 months.

So for timing-wise, we had a limited exposure when we initially assessed the safety of these, so all the safety data that you are primarily seeing is really within that first 6-to-9-month window.

I will say that as part of the reviews for that, we also looked at the time to onset for a lot of the PI3K associated toxicity, so based on the data that is in the respective labels for these agents, typically -- actually, I can just go through each one.

For instance, for grade 3 or greater diarrhea

or colitis, the median onset was anywhere from 3 to 6 months across the four agents. For hepatotoxicity, that seems to be a signal that occurs typically earlier, so it's typically within the first 2 to 3 months of therapy if patients are going to experience hepatotoxicity.

Pneumonitis was much more variable, where we saw a median onset typically around 4 months, but patients that had late onset, all the way up to 19 months for pneumonitis. For patients that experienced PI3K associated rash, typically it was within 2 to 4 months, based on the data that is in the labels.

Those are the main data that we have in regard to timing. Maybe I'll pause there before I get into the design considerations that you had mentioned regarding continuous administration versus something different.

DR. NIEVA: Thank you.

DR. GARCIA: Thank you.

Dr. Cheng, please present your question.

DR. CHENG: Great.

DR. RICHARDSON: Sorry. This is Nicholas Richardson. Can I address his design comment? Is that ok, Dr. Garcia?

DR. GARCIA: Absolutely. Please proceed.

DR. RICHARDSON: Nicholas Richardson again, FDA. As far as design, you make a good point. PI3K inhibitors are intended to be given continuously until progression or unacceptable toxicity, and a lot of the randomized trials that are noted utilized comparator arms that were typically fixed-duration therapy.

So it's not a design that we encourage because we do acknowledge that there are differences when you are evaluating a continuously administered treatment versus a fixed duration treatment. However, the designs as they were conducted do allow us to have an appropriate comparative assessment of these two types of administration and do adequately quantify the risk. However, it is not a typical design that we encourage, just given that the differences in administration can impact the interpretability of the results of the trial.

DR. GORMLEY: This is Nicole Gormley. I'd like to just add on to that and, again, I think this is a really important point.

When we talk about dose optimization, we are including optimization of the dose and exposures, but also looking at schedule and administration. And it's quite conceivable that the continued administration until progression undoubtedly contributes to the toxicity that we're observing. So when we're talking about dose optimization, the schedule should also be considered as part of that optimization to ensure that it's ultimately tolerable and adequately safe for patients. Thank you.

DR. NIEVA: Thank you.

DR. GARCIA: Just to make sure, Dr. Nieva, did these comments address your questions?

DR. NIEVA: Yes. Fundamentally, that's the issue here; is the excessive toxicity for these agents built into this design of treatment to progression? But it sounds like the duration was not much longer beyond when maximum response would be achieved, although for some of the agents, it was

significantly longer than others.

DR. GARCIA: Well, we'll move on.

Dr. Cheng?

DR. CHENG: Thank you, Dr. Garcia.

Jon Cheng, industry rep. This is a question for either Dr. Gormley or Dr. Richardson.

My first question, thank you for a very nice weighing out the situation, but in the appendix, the idelalisib study in CLL I think had a overall survival hazard ratio of 0.34 on table 15, I think. So I'm interested in understanding how the FDA is viewing that result, which is a relatively positive overall survival hazard ratio, although I appreciate the numbers might be small in the greater context of a potential toxicity class effect risk, because obviously there was a withdrawal in other indications.

My second question is a little bit trying to understand -- I think you make the case for Project Optimus and the importance of understanding exposure-response. My question is, does the FDA have a perspective on this post-optimiziation? Is it per

indication or is it per agent? Because there are a number of indications within hematology, let alone outside of hematology; so how does one approach a project in optimization of the dose.

Is it specific to an indication and therefore it has to be defined per indication, or is it per the molecule? It just would be helpful to understand the FDA's perspective.

DR. GORMLEY: Thank you for the question, and there are several questions there, one about Project Optimus and dose optimization versus for an indication; versus the molecule; and then thirdly I believe you asked about the idelalisib 0116 trial.

If it's ok first, I'd like to ask Dr. Brian Booth to present a little bit about what we're thinking about and what we mean by dose optimization just to ensure that there's a level setting here and we're all on the same plane as to what we're really talking about when we talk about the concepts of dose optimization.

Dr. Booth, would you mind presenting a little bit about what we mean by dose optimization and also

Project Optimus?

DR. BOOTH: Certainly. Good afternoon.

Can we please bring up slide 182? Again, my name is Brian Booth. I'm the director of the Division of Cancer Pharmacology I in the Office of Clinical Pharmacology at the FDA. Thank you.

With respect to dose selection for oncology, we generally pursued an MTD approach, however, we have many examples of oncology drugs with significant toxicities, including the PI3K inhibitors that require dose modifications or dose interruptions in a post-approval setting. So we need to reconsider our approach to dose selection and think more about dose optimization for oncology drugs, especially with the current therapeutic options that are available such as targeted therapies.

To illustrate this thought, the figure on the left depicts the exposure-response curve for cytotoxic chemotherapy. Given the mechanism of action, you can see that the curve for toxicity closely parallels the curve for efficacy. It's not possible to distinguish between the two curves. In

this case, it makes sense to pursue the dose based on the MTD concept. This maximizes efficacy, although at the expense of managing toxicity. However, with targeted therapies such as the PI3K or TKIs, the curves on the right are typical of exposure-response relationships that we see.

Generally, we see an earlier plateau for efficacy followed by a more gradual later increase in toxicity, so pursuing the MTD approach with these types of drugs doesn't make sense, especially for drugs [sic – patients] with longer survival and require longer periods of continuous drug treatment. In these settings, management of toxicity of the drug has much greater significance.

What are the implications of these exposure-response relationships for dose optimization? Generally, we maximize efficacy before toxicity. This especially is true if we use an MTD approach. The efficacy is plateaued, and increasing the dose further does not result in any further improvement in efficacy.

In this context, we can say that the

exposure-response for efficacy is flat, however, the exposure-response for toxicity is still on the rising portion of the curve and changes in dose can impact the rate and severity of adverse events. In these situations, we may be able to reduce the dose without impacting efficacy significantly while reducing adverse events.

Recently, the Oncology Center of Excellence launched Project Optimus. This project was initiated based on the recognition that many oncology drugs require dose adjustment and may lead to suboptimal therapy. The mission is to find doses of oncology drugs that maximize efficacy and tolerability, and one of the specific goals is to leverage the nonclinical and clinical data to better select these doses.

In this slide, the traditional approach to dose selection in oncology, based on the finding of the MTD, is depicted. Generally, there is a dose escalation trial designed to identify the dose with DLTs, and subsequently the MTD. The MTD is then used in subsequent registration trials, which may be

randomized-controlled trials, but frequently single-arm trials that are part of the accelerated approval pathway.

With the MTD approach, the assumption is that higher doses will have higher efficacy which then maximizes the efficacy at the expense of toxicity. Generally, a 3-plus-3 design is used, so there are a limited number of patients to assess the pharmacokinetics and pharmacodynamics, safety, and efficacy at each dose level and the observation period to assess DLTs and toxicities is often too short to obtain useful information on dose modifications, including dose interruptions, reductions, and discontinuations.

In contrast, the dose optimization strategies like the one depicted here has a higher chance of identifying the dose with a benefit that outweighs the risk. We began with the same dose escalation design, but with the purpose of better understanding the pharmacokinetics, pharmacodynamics, safety, and efficacy at each dose level. This will often include dose expansion of several cohorts to generate these

additional data at promising dose levels. Further, in this paradigm, longer periods of observation are incorporated to assess adverse events, including the onset of delayed toxicities in contrast to the MTD approach.

Additionally, with dose optimization, there are some more specific recommendations that should be evaluated in order to better select the dose or doses for development. Consideration should be given to nonclinical data such as in vitro or in vivo receptor occupancy or enzyme inhibition because this provides support that the concentrations of the doses selected are in the right range.

In early trials, sufficient PK sampling in a sufficient number of patients is necessary to adequately characterize the pharmacokinetics in order to understand behavior of the drug and any PK limitations such as saturable absorption and to develop exposure-response relationships. This data is also important in identifying exposure-response relationships of biomarker data, as well as with the safety and efficacy data in early trials to better

assess optimal doses.

These exposure-response relationships can also be used to predict patient outcomes by dose level, which can also aid in selecting doses for development. Unlike the MTD approach, there should be some expansion of several promising dose cohorts with sufficient numbers of patients to better understand and evaluate the PK, safety, and the efficacy.

Another important approach that should be considered is to conduct randomized, parallel, dose-response trials, which ensures similarity of patients at each dosage and aids in the interpretation of dose and exposure-response relationships. Finally, another possibility that can be considered is to include multiple doses as part of the registration trial.

With respect to dose optimization combinations, this can get quite complicated, but the following are some general recommendations to consider. First, simply taking the approved monotherapy dosage and applying it in combination

with another drug is likely to cause excessive toxicities, and some dose exploration is warranted. When combining two new drugs, a thorough understanding of the PK, PD, safety, efficacy, and the exposure-response relationships for safety and efficacy for each drug should have been assessed as described for monotherapy.

For two new drugs, there should be dose exploration with different levels of each drug. It may be appropriate to conduct more dose exploration and use combinations with the drug that appears to be more active or more toxic. If a new drug is to be added to an add-on therapy, it may be appropriate to consider some dose exploration with an established regimen in addition to the new drug.

Another point that should be considered is that in the combination study, smaller dose increases than those tested in monotherapy, dose escalation trials should be assessed. As with monotherapy, exposure-response curves for safety and efficacy should be evaluated in each drug in the combination.

Lastly, occasionally drug-drug interactions

occur between two drugs in the combination, which can result in higher exposures than anticipated, particularly in steady state, which may cause unexpected or unwanted toxicity. The dose exploration optimization studies should also provide a provision for assessing DDI liability. Thank you.

DR. GORMLEY: Thank you.

This is Nicole Gormley. I think we've sort of already touched a little bit on your second question, as well, about whether or not dose optimization is indication specific or if it's molecule specific. Really, it's a little bit of both.

For dose optimization, generally, we should always be incorporating information gleaned from earlier stages. What I mean by that is oftentimes we'll start in a broader population initial dose escalation and dose finding, but once specific indications are identified, there may need to be dose escalation and optimization that's conducted separately.

For example, a different dose may be optimal

for an AML population that may be very distinct from what's needed in an indolent follicular lymphoma population. But hopefully, again, when new indications are explored, information from prior studies should be incorporated into those dose optimization studies. Again, though, if you're looking at follicular lymphoma versus marginal zone, there may not be that many differences needed.

The other aspect that comes into this, which Dr. Booth already touched on, is when these products are then studied in combination, the need to, again, really make sure that the various aspects are considered and that separate, really, dose optimization is needed when looking at something as a monotherapy or in combination for a new therapy or a new indication.

I'd like to make sure that we address the third question, which was about the 0116 study, so I'll ask Dr. Richardson to comment on that.

DR. RICHARDSON: Hi. This is Nicholas Richardson, FDA. Thank you for the question regarding the idelalisib 0116 trial. Just as a

refresher, this was a randomized placebo-controlled trial looking at idelalisib plus rituximab versus placebo and rituximab in patients with relapsed CLL, and this is what supported the approval of idelalisib in combination with rituximab for these patients.

For the overall survival information, you are correct that the overall survival hazard ratio for this trial showed a favorable effect favoring the idelalisib arm with a hazard ratio of 0.34. As far as the interpretation, the OS information, as you noted, was still a limited number of events and it was very early information.

The trial was terminated early following the statistically significant impact on PFS, so we didn't have longer term follow-up to ultimately assess the overall survival information, but when we did evaluate the data that was submitted, it was actually very unclear as far as what factors accounted for the difference in overall survival.

Just one note is patients on the placebo arm were able to cross over and receive treatment with idelalisib following progression, which does impact

the assessment of overall survival. So it's a little bit unclear as what accounted for the difference in overall survival in this trial, and interestingly, it's a little bit of a standout compared to some of the other trials that we had discussed during the presentation.

DR. CHENG: Thank you for that. Yes, that does answer my question. I did want to make an aside. I appreciate the helpfulness in optimizing each dose or each indication combination, however, that does take time and resources, so those are just factors to at least be aware of.

DR. GARCIA: Thank you, Dr. Cheng.

We'll move on. Dr. Thanarajasingam, please, your question?

(No response.)

DR. GARCIA: Dr. Thanarajasingam, you may be muted. Pleas unmute.

DR. THANARAJASINGAM: Yes. Sorry about that. I have two questions. The first is about toxicity and tolerability, and the second is unrelated and is about these drugs addressing an unmet need.

Dr. Richardson, in answering Dr. Nieva's questions, you had outlined some information about the timing to toxicities. That's very difficult to find published or systematically reported anywhere by sponsors or the FDA. We know from clinical experiences that these PI3-kinase inhibitors have short- and long-term toxicities and some of the immune-related AEs can be delayed. When these agents are chronically administered, even low-grade AEs that are protracted can affect tolerability.

So when you're talking about dose optimization, do you think that going forth in drug development -- sort of related to the presentation that was just given that was really helpful -- with this class of agents, do we need longer dose-finding studies, or DLT windows that include patient-reported outcomes, which we know are needed to understand tolerability?

I guess my question is, does the FDA have the authority to require these types of studies and also require the reporting of not only high-grade AES, but the timing of the lower grade AEs that may be

impacting tolerability, and require high quality PRO studies assessing multiple domains of tolerability in this setting? It just seems like this is very important complementary information to the traditional survival outcomes with this particular class of drugs.

That is the question about toxicity of tolerability, a lot packed in there, but the second one is a bit more straightforward.

Of the trials you discussed, we're looking at trials in multiple biologically distinct disease groups, and at times in different lines of therapy, different populations. To address the question of whether these drugs address a high unmet need in CLL, to your knowledge, and I supposed to my other colleagues on this panel, has there been any trial of PI3-kinase inhibitors in patients with double-refractory CLL; that is those who have progressed on a BTK inhibitor and venetoclax? Thank you very much.

DR. GORMLEY: Hi. This is Nicole Gormley. I'll ask Dr. Richardson to respond. Thanks.

DR. RICHARDSON: Hi. It's Nicholas Richardson, FDA. Thank you for the question. I'll address the tolerability question first.

One thing you had mentioned is, I think, in early-phase trials, how do we look at toxicity and tolerability, and given the lessons learned from the PI3K inhibitors, how can we improve that process? And you had mentioned several things.

One is, in early-phase trials, a lot of times we identify a dose to carry forward based on an evaluation of dose-limiting toxicity, and you had specifically mentioned the DLT window. Typically, a DLT window is one cycle, and that is reasonable when you typically have a drug that is administered daily, or twice a day; for instance, copanlisib is administered once a week for 3 weeks with one week off, to really get a sense of dose-limiting toxicity.

However, that does not incorporate the assessment of later onset toxicity, which we do see with these agents. Specifically some of the immune-mediated toxicities that are grade 3 or greater, we know can have a later onset based on some of the data

that we have, even up to 6 to 9 months.

One thing that is something that we do to try to work in collaboration with the sponsors is the way that the totality of data is evaluated to really look at these early-phase trials and the data generated regarding safety, PK, PD, exposure-response, and preliminary activity. If we do have data, or if there's previous data with a same in-class agent that indicates that later onset toxicity is a concern, typically we try to at least have a proposed plan of how that will be captured in the assessment of safety in these early-phase trials.

So it is a consideration and something that we do try to encourage sponsors to incorporate when they're really looking at all the available safety and PK and PD information when they are selecting a dose to carry forward.

Then you had mentioned patient-reported outcomes and whether that should be included, and just give me a second while we pull up a slide.

As part of an initiative within the Oncology Center of Excellence, we spend a lot of time and

effort really looking into how the patient voice and the patient experience can be incorporated in all aspects of drug development. In early-phase trials, we do recommend and encourage that patient-reported adverse events be incorporated because it does help inform tolerability.

You do have the ability to assess these outcomes, even in early-phase trials and even in registrational trials, to really get a sense of tolerability from the patient's standpoint. There's been a lot of work done on the different measures of assessment that can be incorporated in these trials for the particular population that is being evaluated and is something that we encourage in all aspects of drug development.

So I'll pause there and just see if any of my other FDA colleagues have any comments before addressing the double-refractory CLL population in PI3K inhibitors.

DR. GORMLEY: Yes. Thanks. This is Nicole Gormley. I would just add on, your question was specifically as to whether or not we had the

authority to require further or more aggressive dose optimization, or authority to require patient-generated data or patient-reported outcomes, and the short answer is, no, we do not.

I will say, though, as was pointed out earlier by Dr. Cheng, dose optimization does require additional resources, and it does require additional time. In our experience, though, and what we're seeing here in the PI3-kinase inhibitors and in other areas is that it's time well spent. The investments that are made in finding the right dose, they improve outcomes for patients, and then it results in a better product in the end that allows us to have confidence in the results from these studies. So while it's not something that's within our authority to require, it's something that we strongly recommend and encourage.

Also as well, related to the patient-reported outcome information, it's crucial to have his information about how these products impact patients. It's helpful to collect this information early, but it's also most robust when it's captured in

randomized trials. So we encourage sponsors as well to capture this information but, again, we don't have the authority to require it.

Thank you. I'll turn it back to Dr. Richardson to address the CLL question.

DR. RICHARDSON: Hi. Nicholas Richardson, FDA. Thank you for the question regarding double-refractory patients with CLL who are refractory to a BTK inhibitor or a BCL-2 inhibitor.

As you know, BTK and BCL-2 have changed the treatment landscape for CLL. The development, at least of the approved PI3K inhibitors, was really prior to the treatment landscape or in conjunction with the changing treatment landscape.

We do have limited data at the time, however, there are ongoing development of products in this class, and there is clinical trials that are currently underway that do allow these patients to enroll, given that they have failed two therapies that have known efficacy and safety, and some trials showing a survival advantage.

DR. THANARAJASINGAM: Thank you very much to

both of you. I appreciate the responses.

DR. GARCIA: Thank you.

We'll move on. Dr. Advani, please state your question.

DR. ADVANI: Thank you. This is Dr. Advani from Stanford. To anyone from the FDA, most of these were global trials, so were there geographic differences in overall survival? Was it all across the board or was it in underdeveloped areas?

The second question is, how many of these were recent, in the last 2 or 3 years, where all these trials are reporting out and related maybe to the pandemic and the supportive care differences in different parts of the world?

DR. GORMLEY: Thank you. Thank you very much for the question. I'll have Dr. Richardson answer this question. Thank you.

DR. RICHARDSON: Hi, Dr. Advani. Thank you for the question. I will freely admit, I don't think we have a very, at least, data-driven answer for you. We'd have to go back and look. We typically do look, as far as a sensitivity analysis based on region,

typically, for the primary outcomes at least in the randomized trials of PFS and OS. Within a single-arm trial, we do in addition look at region based on response rate.

As far as specific data points, I'd have to look it up for you, but there have been no overall regional differences that would prompt concern regarding differences for the U.S. versus outside of the U.S., although I will say, given the comparator arms that were chosen, some of the trials did have an imbalance where there was the majority of patients enrolled ex-U.S. and a limited representation of U.S. patients.

DR. GORMLEY: This is Nicole Gormley. Just on the first part of the question about the global aspect, just another consideration here is that, as we've highlighted, these analyses that we're talking about are really early, several of them, so it's hard to do additional subanalyses of the overall survival based on those results. When we look at toxicity, though, overall, especially as Dr. Richardson highlighted, we do do analyses to look to see if

there are regional differences or things like that and, again, there's nothing that grossly stands out related to that.

Perhaps I'll start with the COVID question. Some of these trials were conducted before the COVID pandemic, so were not impacted, and that's the case with the vast majority of these trials. Some of the trials have been conducted more recently with COVID, where COVID could have had an impact.

I will highlight, though, that what we're talking about here are randomized trials, so even though COVID may be occurring during the time frame of the clinical trial itself, randomization should control for any imbalances or differences, things like that. We feel confident that this is not just a finding that's related to the underlying COVID pandemic. Then as mentioned, most of these trials were conducted before the COVID pandemic started. Thank you.

DR. ADVANI: Thank you.

DR. GARCIA: Okay. We'll move on.

Dr. Kraft, you've raised your hand?

DR. KRAFT: Walter Kraft. I had put my hand down because Dr. Booth had addressed most of the issues, but I will ask specifically about biomarkers. This is about a specific class of medications.

For dose optimization is there a biomarker that could serve as a surrogate towards a clinical endpoint that would optimize or help with the dose optimization across these drugs within the single class?

DR. GORMLEY: This is Nicole Gormley. I'll start the response and then open it up to other FDA colleagues if there are others that want to chime in.

I would say that in terms of biomarkers for endpoints for response assessment, that has not been uniformly developed across the class, and there may be other markers that are helpful for dose optimization that could be looked at, et cetera. But again, to my knowledge, there's nothing that's been uniformly done.

DR. KRAFT: Thank you.

DR. GORMLEY: Thank you.

DR. GARCIA: Great.

The next question is Dr. Au.

DR. AU: This is Jessie Au from IQSP. I have a question regarding toxicity for this class of agents, especially in the context of dose optimization, and particularly for the combination therapy. I think Dr. Booth and Dr. Richardson probably can help me here.

When I look at the data that Dr. Richardson presented today, as well as the briefing materials that were sent to us earlier, what is clear is the single agent's data, idelalisib, when I compare that to the data in the randomized trial, with the combination therapy, there seemed to be a very substantial pharmacokinetic interaction in the sense that the AUC that I saw on those graphs were very, very different, like 200 percent higher in the combination therapy, even though the combination therapy was using a lower dose.

Secondly, at the same AUC level, the toxicity to the GI was, again, almost twice as high. And I'm wondering if I'm reading the data correctly, and if I read it correctly, then is this something that's

common for this class of agent? Because if it is, then this class of agent may be teaching us a big lesson. And that is that this agent, because of the mechanism of action and many downstream effects, may be actually causing very substantial PK/PD interaction on the host tissue level, which means for this class of agent, it will be a real big problem when they develop combination therapy and not do the dose optimization.

So my question is, number one, am I reading the data correctly? Maybe Dr. Booth can help me there. And number two, would that be the same conclusion, and how do we deal with agents such as this? Because it has such a broad mechanism of action, many downstream effect, and when you see PK/PD interaction at such a high level, how do we deal with it, from the dose optimization standpoint?

DR. GORMLEY: This is Nicole, Gormley. Thank you again for your question. I will ask Dr. Booth to respond.

DR. BOOTH: Hello. Good afternoon again. I'm not quite sure what you're specifically referring

to, Dr. Au, from the data, but one of the concerns that I brought earlier, at least sometimes, is that we put this under combination, and we can end up having a drug-drug interaction, and that can raise the exposure of one of the drugs. If you don't look at the situation long enough, you may not be aware of that, and you can end up having exposures that are higher than anticipated that can confound or lead to these unwanted toxicities later in therapy.

DR. AU: Yes, I'm sorry. I was referring to figure 4 and figure 9 in the briefing materials. One shows the single agent's PK and the toxicity, and the other one shows the combination therapy. And what caught my eye was the much, much higher AUC in the combination therapy and a much more severe toxicity, even at the same AUC. But I think you're right; there's probably a DDI going on, but I don't know how the PD interaction becomes so severe.

I cannot refer you to the slide because figure 9 was not on the slide. Figure 4 was on slide 49 of Dr. Richardson's presentation.

(Pause.)

DR. AU: On the left panel, right; this is the single-agent plot. So if you go to the combination therapy plot, which is not on here, you will see double the AUC, and not only that, the probability for toxicity, that the same AUC becomes twice as severe, which to me says that's PK/PD interaction on both the effect level and on the kinetic level.

DR. BOOTH: Right. I think we're on slide 133.

DR. AU: Yes, this is the combination. If you look at the same AUC, about 15,000 units, which is the one on line 49 for single agent -- same agent -- it was 20 percent probability, and now it's about 40 percent probability. So somehow it could be the delayed effect you're talking about, where the immune system is adding up as well, but you're seeing at least an additive effect, I think, with the other combination agents.

DR. BOOTH: Yes, potentially.

DR. AU: Yes.

DR. BOOTH: I would also like to invite

Dr. Lian Ma with the pharmacometrics group to see if she has any additional thoughts on these analyses.

DR. MA: Hi. This is Lian Ma from pharmacometrics at FDA. Yes, another potential explanation for the difference in the exposure scales, it could be that the exposure metric is slightly different. For the monotherapy plot, the exposure I think is relating to AUC for dose 1, and for this one, it seems to be AUC within 24 hours.

So there might be a slight difference in how to derive the AUC metric. But again, I think I agree with your comment that the substantial increase or difference in even the toxicity rate could be partially due to the overlapping toxicity between the two agents in the combination.

DR. AU: Thank you. I think what this data basically said to me is it's this class of agents is special, and it will help me on my vote. Thank you very much.

DR. MA: Thank you.

DR. GARCIA: Thank you both, the FDA and Dr. Au.

Moving next to Ms. Nadeem-Baker.

MS. NADEEM-BAKER: Thank you. This is Michele Nadeem-Baker, and I have a follow-on question to what Dr. Gita was asking. And that is, I know that in both Dr. Gormley's and Dr. Richardson's presentations, they talked about there being a variety of options for patients of drugs, specifically CLL and SLL patients, to take. But within those, once patients develop resistance or perhaps if they had comorbidities, those drugs are not viable options.

I do realize that some but not all mention that a patient to go on one of these needs to have two or more previous treatments, but I don't see that across the board on all of them. Is that something that would be made specific to this class of drugs in the future, and therefore they could still be used as an option when patients run out of others, short of a clinical trial?

DR. GORMLEY: Thank you. This is Nicole Gormley again from the FDA. Thank you very much for the question, and I think you bring up a really

important point, and this is something that we spend a lot of time thinking about because you are absolutely right; patients do relapse or, unfortunately, sometimes develop refractory disease, and there is a need for additional therapies for these patients.

However, when we're in that sort of situation, it's really important that the drugs that patients receive, even if they have exhausted all other therapies, that we know that these are safe. So we would not be in a situation where we would just change the indication for a class of products if we didn't have data in that population.

Thank you for displaying this slide. Just to answer your question a little bit about some of us have different lines, et cetera, some of this was just a temporal factor here in that these were approved over various time points, and then different therapies became available. We're talking about quite a time span from the approval of the first one to the last one, so some of these just represent changes in treatment landscape during that time.

I guess I would underscore, though, that when we're looking for therapies for patients, we still need to have confidence that they are safe and effective, and we would not adjust an indication without having data to support them. I hope that answers your question.

MS. NADEEM-BAKER: Thank you.

Thank you. And I have an additional question, which is regarding things like on page [sic – slide] 14 of Dr. Richardson's presentation, when there are things added on PMRs such as regarding a drug such as the Dear Healthcare Provider Letter and boxed warning.

Does the FDA provide any oversight on how prevalent these communications are, and is there any education that's also a requirement of the company for the providers and patients to ensure that they are understanding, and they're reading these, and that they actually get to them, and that they're understanding -- because this is more for outside community physicians -- what these mean?

DR. GORMLEY: Thank you for your question. I

guess I would just start by saying I think you bring up a very important point in terms of, specifically, how is information disseminated to providers.

When a drug is approved, we issue and include information -- prescribing information or the label, the PI -- about the safety, risks, et cetera. In certain instances when there are significant safety findings, we will include warnings and precaution or a boxed warning.

Several of these products were approved with a REMS, a communication REMS. I can't provide the specifics of what was included within the REMS at this time, but they include information or require that there be communications to prescribers, and there is ongoing assessment of that communication as part of the REMS. Those are actions that can be taken at the initial time of approval.

When we were made aware of some of the findings, for example with idelalisib, the FDA issued a safety alert, and that goes through various channels. It's placed on the FDA website, and there are distribution lists to providers and medical

professional societies associated with that to make them aware of new safety findings that we become aware of.

Often then, sponsors will issue a Dear Healthcare Provider Letter that goes along sometimes with the FDA safety alert or can be issued on their own as well. We think that it's really important that these Dear Healthcare Provider letters are issued broadly to providers and, again, medical societies, et cetera, to ensure that that information is widely communicated and available to providers.

We engage with sponsors to ensure that that happens, but it is within the sponsor's purview, so to speak, to figure out, initially anyway, the distribution. If we feel that the distribution is not adequate, we will or can pursue other avenues for FDA then-led [indiscernible] communication. But I think it's of the utmost importance that providers and patients be aware of safety findings with these products.

MS. NADEEM-BAKER: Thank you. I have no further questions.

DR. GARCIA: Thank you.

I know Dr. Diehl, Dr. Cristofanilli, and Dr. Dunleavy have a few questions. Maybe in the interest of time, for us to stay on track, we can actually save those questions for our section after the OPH session.

Please, Drs. Diehl, Cristofanilli, and Dunleavy, just bear with me. Hold those questions for a little bit later, and I promise you we're going to start with the three of you during that session.

We will now take a quick 10-minute break. Panel members, please remember that there should be no chatting or discussion of the meeting topic with anyone during the break. We will reconvene at 2:15 p.m. Eastern Standard time. Thank you.

(Whereupon, at 2:04 p.m., a recess was taken.)

DR. GARCIA: We're going to go ahead and start again. I would like to state into the record that no one registered to speak for the open public hearing session.

We will now take remaining clarifying

questions for all the presenters. Please use the raised-hand icon to indicate that you have a question and remember to put your hand down after you have asked your question. Please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can.

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

Just to get back to the three pending questions that we have from the earlier session, we're going to go with Dr. Diehl.

If you don't mind, ask your question.

DR. DIEHL: Lou Diehl, Duke University.

Dr. Booth talked, in dose optimization, about a randomized trial, which immediately begs for me the second question, which is how do you select the lower dose? We know how to select the upper toxic dose,

but how would you select the lower dose?

The second part of the question, is there enough information in the phase 1 trials that would tell us where toxicity starts and where efficacy starts to actually make a guess at what that second dose would be?

DR. GORMLEY: Thank you.

DR. DIEHL: I end with the presenters, yes.

DR. GORMLEY: Great. Thanks. I'll ask Dr. Booth to start. Thank you.

DR. BOOTH: Thank you for the question. I think in my presentation I listed a number of bits of evidence that we can rely on to help make some decisions about what sort of doses to look at. Some of this will be from the interactions with PI3K inhibitors or receptor occupancy, that sort of thing, and give us some indication of whether we're in the right ballpark. We could also use some of the PK/PD information that comes out from some of the early trials.

For instance, let's try slide 139, just as an example. This is for duvelisib. They had these

models where they were looking at the different doses and concentrations on the p-AKT suppression, and there are some models. You can see very early on that the 25 milligram gave them almost complete suppression of this biomarker, so that helps us to better understand what dosing in vivo is going to be in the right ballpark.

Further, you'd have to look at what you see in the early clinical trials in terms of the safety and the efficacy that comes out of that, and evaluate all of that, and make some decisions about what doses you're going to take forward.

I would invite others to chime in on that if they have other things to add.

DR. DIEHL: I guess the other part of my question is, does that actually correlate with outcome, either toxicity or efficacy?

DR. BOOTH: Well, to some extent it certainly does. We know that duvelisib seems to have some activity at that level. We can't use one single piece of the information to make that decision. I think you'd have to look at this in terms of the

collection of information and the differences that you've looked at, including the in vitro and the nonclinical [inaudible], as well as the early data from the trials that you get.

DR. GORMLEY: This is Nicole Gormley. I think I'd like to just add on. I think we find ourselves in a situation where we have some early data to suggest, for several of these products, that lower doses may have been equally effective. But the issue that we find ourselves with, with across the class, generally, is we don't have lots of data or robust data at the lower doses.

I think that's where a randomized dose-finding trial or randomized phase 2 trial could really be helpful, spending a little bit more time at dose optimization where you're collecting more robust data at lower doses compared to the higher doses for both efficacy, safety, tolerability, and patient-reported outcomes in a randomized dose-finding setting, and you'd be well prepared to go into a trial for registration, having confidence in the dose that's been selected.

Then we would know definitively whether or not that lower dose, or whatever dose -- the best optimized dose in a randomized trial -- what the efficacy, and safety, and the ultimate clinical benefit would be from that randomized trial that would then be used for registration.

DR. DIEHL: I don't want to play the devil's advocate, but would you really know that, if you only selected two doses to use?

DR. GORMLEY: I mean, you may never perfectly know that you have the best dose possible, but I think we would know that we would have more information than what we currently have. I think it would have to be informed by the early initial phase 1 dose finding, et cetera. I think you can have inklings then, or more information if you had a randomized phase 2 and, again, selecting the winner, so to speak, but then also gleaning more information.

I guess I would just add that dose optimization really can be done throughout a drug development course, looking at the initial phase 1 trials, and then randomized phase 2 trials where

you're gathering more information. Then even in the phase 3 trials, additional aspects or things can be done to make sure that you have the most optimized dose, making sure that the schedule and other supportive medications, et cetera, are adequate. I think that this can be paid attention to. And you're right; at some point we may never know that we have the best dose, but I think we'd be in a much better situation than what we are now.

DR. DIEHL: Yes. Thank you very much. That relieves my mind a little bit on the question.

DR. GARCIA: Thank you. We move on to Dr. Cristofanilli, please?

DR. CRISTOFANILLI: Yes. Hi. This is Dr. Cristofanilli, Weill Cornell, and I have a question for Dr. Richardson.

You did a great presentation and went over toxicity, and that's because you have the studies, as well, that remind us that the overall survival is an objective endpoint. As you know, many times it's not only a matter of toxicity affecting the overall survival, but also the subsequent therapies and the

ability to really continue treatment with an efficacious agent. We're saying a disabling disease should have a number of different options.

Do you have any information in the randomized studies about the number and the type of therapy that this patient received after they were off the drug or they progressed? Because it seems to me that it may certainly be an issue related to the dose, but it could also be an issue with this class of drugs with a specific target that may affect bone marrow or may affect the liver function at the point that you are unable to continue treatment. When it is a chronic administration, it is also affecting the administration of the other therapies. Thank you.

DR. GORMLEY: Hi. This is Nicole Gormley again. I want to make sure I understand and make sure we adequately address your question. Your first question was -- and correct me if I'm wrong -- that it's not necessarily easy to ascertain what the cause of the overall survival findings may be; that it may be due to toxicity or --

DR. CRISTOFANILLI: Yes. I think, in

general, the overall survival, when you have one intervention, it is due to a number of factors. There's not only one therapy, but the accumulation of therapies that that patient receives, particularly in an indolent disease; so 5 or 6 lines of therapies before or after the agent has been studied. But if you do have an agent that affects their ability to receive subsequent therapies, or affects the efficacy of subsequent therapies, then you have another issue that you have to deal with.

Do we know how many therapies and which type of therapy this patient received after they complete the treatment either for toxicity or for progression?

DR. GORMLEY: Yes. First, I'll just mention just briefly about your overall survival comments. This is Nicole Gormley again. You are absolutely right in that overall survival is really an assessment of multiple things.

Overall survival can be impacted by inadequate dose, perhaps, and too many toxicities. It could be just related to the toxicities of this class. It also could be an impact on patients that

result in inability to tolerate subsequent therapy or inability to respond to subsequent therapies, so overall survival really is an assessment of multiple factors and impacts of the drug.

I'll ask Dr. Richardson to comment about your other question in terms of subsequent therapy that patients may have received after participating in the clinical trials.

Dr. Richardson?

DR. RICHARDSON: Yes. Hi. Nicholas Richardson, FDA. As Dr. Gormley mentioned, this is a good question. As we mentioned, just using the PI3K inhibitors as an example, overall survival we look at from an efficacy and a safety standpoint.

As we went through in the presentation, nearly all these trials had an advantage in PFS or overall response rate, which really sort of makes us focus on the safety aspect of overall survival. One thing that you mentioned that's really important in the setting that we're talking about today -- patients with CLL or indolent non-Hodgkin lymphoma -- is they are considered indolent diseases,

and patients do have the ability to receive multiple subsequent therapies.

So when we do look at overall survival to really sort of address the impact of subsequent therapy, we go about it looking at what death events occurred while on therapy or within typically 30 days within the last dose of therapy, so essentially a treatment-emergent event.

The other thing that we look at is whether there is a temporal association with the fatal outcome. Just as an example, we know that some of the PI3K inhibitors cause dermatologic toxicity. We've had cases where patients have experienced either a grade 3 or grade 4 rash event, and then that rash subsequently became infected, and ultimately the patient succumbed due to infection. So if there's a temporal relationship, we also consider that when we are evaluating the reasons for death.

To address subsequent therapy, we do ask sponsors to provide us information regarding the timing of subsequent therapy, and if available, we do request information on the specific types of

subsequent therapies so we can get a sense of just what you mentioned, does the therapy that's being evaluated in a trial either impact their ability to receive subsequent therapy or does it impact the ability to respond to subsequent therapy? As you mentioned, PI3K inhibitors are immune modulators, so there is a concern in regard to subsequent therapies and how patients may respond.

So we do evaluate all of that to really try to get a sense and fully characterize the overall survival information from these trials.

DR. CRISTOFANILLI: Thank you.

DR. GARCIA: Thank you.

Dr. Dunleavy, do you have a question?

(No response.)

DR. GARCIA: Dr Dunleavy, you may be muted still.

(No response.)

DR. GARCIA: Alright. Let's just move to the next question.

Dr. Conaway?

DR. CONAWAY: Yes. I'd like to express how

important I think Project Optimus is and the need for dose optimization. I think really the central issue here is the choice of dose that went into some of the early studies. At Virginia, we have a center for early-phase trials that's researching, advocating, implementing dose optimization designs much along the lines of what Dr. Booth laid out.

I wanted to point out in response to some of the questions, there are statistical designs to handle nearly all of the issues that were discussed today. There are designs for evaluating both safety and efficacy for targeted agents with curves that were depicted by Dr. Booth. There are designs for combinations of agents to explore the surface, multiple combinations of agents. There are designs for late-onset toxicities, heterogeneous groups of patients, and designs that will incorporate patient-reported outcomes, PK data, and biomarkers that would allow you to investigate multiple schedules.

I think that the technology really does exist to greatly improve dose optimization, so I think that

that's an important thing that we should be aiming for. That's a general comment.

My specific comment, in answer to an earlier question, is there's apparently no authority for the FDA to mandate designs, but one concrete suggestion I would like to see is perhaps recommending or requiring operating characteristics of whatever design is used, some measure or some quantification in the degree of uncertainty in the dose that was actually selected, or dose calculations or simulations that might lead to a recommendation to move more than one dose forward.

So I think whatever design is proposed, I think that some degree of quantification of the uncertainty in the results of that design would be very useful. Thank you.

DR. GARCIA: Thank you, Dr. Conaway.

Maybe we'll go back to see Dr. Dunleavy.

DR. DUNLEAVY: Yes. Hi. I apologize about that. I also had a question about toxicity. With this class of drugs, when you see immune-related toxicities and immune-related toxicities that have

been reported in clinical trials, you're particularly struck by the unpredictability of onset of those toxicities. And the question really is, how are host and disease-specific factors interacting with those dose-specific factors and causing dose toxicities?

There have been some observations with this class of drugs that immune-related toxicities are different in different patient populations. They may be different in different age groups. We even talk about follicular lymphoma and CLL. So there are some differences if you look at different classes of agents in those diseases in terms of their biology.

I guess the question is, in the data that we have so far, with PI3-kinase inhibitors, are there any hints of these other factors interacting significantly with dose-dependent factors? And if so, is that something that will need to be particularly considered for this class of drug in moving forward towards developing them further?

DR. GORMLEY: Hi. This is Nicole Gormley. I'll take a first stab at the question, and then I'll open it up to others on the team.

I think you bring up a lot of good questions, and these are things that we definitely looked at, to some degree. I will say we are somewhat limited in that, depending on what factors we're correlating the response with, some of these factors we don't have the most robust information, but this is something that we have seen and characterized.

In particular, you noted that patients -- we see a little bit of an atypical factor or phenomena, that a lot of the toxicities that we see tend to sometimes be worse with the PI3-kinase inhibitors in younger patients or those that have received less intensive therapies previously or newly diagnosed. We have a wide data set here, but it is sometimes hard to pin down specifically what those factors are that are contributing the most or had the most impact with this class of product.

I'll open it up to others that may want to respond from the FDA team.

DR. RICHARDSON: Hi. This is Nicholas Richardson, FDA. Maybe just to reiterate what Dr. Gormley said, you raise an important concept and

question with this particular class, and I guess just two comments.

One, there is some data out there that supports that patients with untreated or treatment naïve disease and/or those that have received less prior therapy may be at greater risk for immune-mediated toxicities, and we have noted that trend in the PI3K inhibitors, and that trend also exists in other immunotherapy agents.

I think it's not clear, but maybe one example is the 0116 trial for idelalisib was in relapsed CLL, looking at idelalisib plus rituximab versus placebo and rituximab. The safety profile and the safety outcomes for that particular trial were different than the 0123 trial, which was evaluating idelalisib in a treatment-naïve CLL population. We have noticed this trend in that regard, in which patients with treatment-naïve disease or less prior therapies do seem to be at increased risk and have numerically higher rates of immune-mediated toxicities.

Then again, I think it also goes back to the specific isoforms, the selectivity of the agents, and

do they impact one isoform versus others, and how that plays a role in the toxicity that we're seeing. Specifically, with this class of agents, the impact on regulatory T cells really seems to be the primary driver of immune-mediated toxicities.

So I think it's a really good question and comment. There is some data out there to support that, and it's something that should be noted and is important as we look at the trials and development of these agents moving forward.

DR. DUNLEAVY: Okay. Thank you very much.

DR. GARCIA: Thank you. We'll move on to Dr. Chen.

Andy, do you have a question?

DR. A. CHEN: Thank you. This is Andy Chen, Oregon Health & Science University.

With the withdrawal of duvelisib, idelalisib, and umbralisib, the only PI3K inhibitor left for follicular lymphoma is copanlisib. From the CHRONOS-3 data that you presented, although the top line had a ratio for overall survival with slightly less than 1, you did point out that there's increased

risk of death from adverse events.

So is there thought on the FDA about having this last option in this class to be withdrawn from market? Thank you.

DR. GORMLEY: This is Nicole Gormley. I can't specifically comment per se on what future regulatory actions will be. I will note, though, that several of the products do remain on the market. Some of these were indications that were drawn such that the entire product was not removed. For example, idelalisib for the treatment of CLL does remain on the market, and duvelisib is also currently on the market for CLL.

I'm not sure if we have a slide that lists everything that's currently on the market, but several of these products do still remain, but these were just indications that were removed. And as you mentioned, copanlisib also remains on the market.

I think where our perspective is and I think our concerns are is that for anything that remains on the market, we have to have confidence that these products are safe and effective and that they don't

do harm. In general, as was stated earlier in our presentations, the onus is really on the sponsors to prove and provide evidence, substantial evidence, that their products are safe and effective, and that is the guiding principle; not how many are on the market, but is the product safe and effective. That's our regulatory standard. And I hope that answers your question.

DR. A. CHEN: Thank you.

DR. GARCIA: Jorge Garcia, Seidman Cancer Center. I have a question for Dr. Gormley.

There's no doubt that we're interested in patients with diseases with prolonged natural history such as the one that we're reviewing today. Ideally, you want to have an earlier initial endpoint that can capture the overall outcome, and clearly, to me at least, it's not clear that PFS is a valid surrogate endpoint for survival with very limited circumstances.

I know in the past the agency has rejected time to treatment failure as a surrogate endpoint, but perhaps -- and my question to you -- since we're

talking about a different class of agents with different mechanisms of action, I think that endpoints then can capture both dropouts due to toxicity, dose discontinuation, or dose reductions, and also tumor progression as events may be ideal for this class of patients.

Would the agency be open to look at different endpoints for this class of agents in particular?

DR. GORMLEY: You brought up a lot of really interesting and important points with the question about what are the appropriate endpoints for this disease space. I'm going to take this in parts, if that's ok.

The very first issue is that, in general, we are very amenable at the FDA to discussing with sponsors what the appropriate endpoints are for their trial design and for their specific product. We're also very open to engaging with the broader community and multiple stakeholders, industry, academia, et cetera, on development of new endpoints, especially early endpoints. That's generally what's needed, is development of earlier endpoints that can

allow for more expeditious drug development.

But when we look at early endpoints and when we use those earlier endpoints, whether or not it's a surrogate or not, or just an earlier intermediate clinical endpoint, we still always also need to look at overall survival, and there are lots of ways that this can be done. But trials ideally with an earlier endpoint of view should continue to be followed for later endpoints such as overall survival such that we can fully assess them, the true clinical benefit from the overall survival assessment.

I'd like actually to have our statistical team -- and I'll come back and make perhaps a few additional comments at the end -- comment a little bit as well about how we look at OS, especially also when it's not the primary endpoint.

I'd like to have Dr. Rodriguez speak.

DR. RODRIGUEZ: Hi. Thank you. My name is Lisa Rodriguez, and I'm the deputy division director for the Division of Biometrics IX at FDA. I will give a brief overview of considerations for overall survival evaluations, in general, and for this PI3K

class of drugs.

Overall survival is an important metric in supporting a benefit-risk determination, so I will refer to OS for overall survival in these slides. Here, we will overview the regulatory viewpoint of this endpoint first.

OS is typically defined as the time from randomization to death from any cause. Randomization tends to balance all factors, known or unknown. OS is a preferred efficacy and safety endpoint in oncology clinical trials. It is an objective measure of clinical benefit and incorporates the impact of toxicity.

When prespecified for hypothesis testing, the nonparametric log-rank test has typically been used as a statistical test for evaluating significant differences in survival between treatments. OS is typically summarized via the hazard ratio in comparison with median survival time. According to convention and oncology settings, hazard ratios are calculated such that values exceeding 1 indicate higher risk of death for the investigative treatment

group. Confidence intervals for the hazard ratio are evaluated in the absence of or in addition to a statistical test.

Other descriptions such as the probability of surviving to set time points can also be useful. A prespecified ITT analysis is preferred for OS, however, we do typically conduct additional sensitivity analyses to evaluate the robustness of the estimates. Finally, OS is an important endpoint because it supports the overall benefit-risk determination for regulatory decisions. It is a safety endpoint, as well as an efficacy endpoint.

Here, I would like to outline some general issues associated with evaluating OS data and safety considerations that may be observed. A long natural history of certain diseases has motivated use of primary endpoints other than OS for efficacy claims due to the time needed to observe a sufficient number of events.

Statistical analysis plans for trials using progression-free survival or overall response rate as primary endpoints have not always included

event-driven, prespecified OS analyses. Because of this, hazard ratio interpretation may be challenging due to patients crossing over to subsequent treatments. There may be potential confounding due to subsequent therapies. There may be a low ratio of events to sample size, and OS is usually considered exploratory in such settings.

OS is a safety consideration, in general, and especially in a situation as we observed in the PI3K inhibitor class, where we can observe the following: a pattern of OS hazard ratios greater than 1, that is more than one study; prior information on risk for a product is informative such as adverse events or risk of death; and there are label warnings for the PI3K inhibitor class.

OS contributes to the totality of evidence on informed safety, even in the absence of statistical testing. So even with early OS data, the observed results, prior safety information, and observed toxicity profile should adequately rule out harm and help support a conclusion that the products are safe.

These are some considerations we use to

evaluate the OS data for the PI3K-inhibitor class and may be useful to consider in general. First, it is useful to consider the available survival information based on the plans and available data; even if none of the studies for this class specified a number of events for evaluation of survival data and there were a low number of observed events, as low as 3 percent of the sample size, leading to uncertainty in estimates.

The estimated hazard ratios and confidence intervals provided descriptive information for the evaluation of potential safety signals. Point estimates for the hazard ratio exceed 1 across multiple studies. Wide confidence intervals do not adequately rule out potential harm. Death rates by treatment arm provide important summaries as well. As we saw from the main presentations, death rates were higher in investigative treatment arms for most of the studies.

In summary regarding evaluation of OS, the confidence intervals for the OS hazard ratio are wide with large upper bounds, however, we can observe that

the large upper bounds indicate death hazards may be up to multiple times that in the control arm. There are higher death rates in the investigative treatment groups and higher OS hazard ratio estimates in several studies across the PI3K-inhibitor class. While there are a low number of events and uncertainty in estimates, when potentially harmful OS hazard ratios are observed in multiple studies in this class, a chance finding is questionable.

In summary, sponsors have an obligation to demonstrate their products are safe and effective. For the PI3K inhibitors, the observed overall survival estimates, especially considering prior information, observed toxicity profiles, and questionable dose selection, do not adequately rule out harm or support a conclusion that these products are safe. Thank you.

DR. GORMLEY: This is Nicole Gormley again. Just to wrap up, I think we are definitely amenable and interested in exploring further endpoints that could be used as earlier time points and that could expedite drug development. I think there are lots of

potential candidates out there that could be useful in this disease space, but if those are used, we still really need to have an evaluation of OS because it's so critical to assessing clinical benefit-risks. Thanks.

DR. GARCIA: Thank you.

I think, Dr. Sung, you had your hand raised. Do you have a question?

DR. SUNG: Sorry. It was answered, but my hand was raised.

Questions to the Committee and Discussion

DR. GARCIA: Great. Thank you.

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 with the questions to the committee, and panel discussion, and vote. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel.

This is question 1 for the committee, and the

task at hand right now is for us as a group -- after a pretty robust session of questions and answers and a great presentation by the FDA -- to discuss the observed toxicity of the PI3-kinase inhibitors as a class and whether randomized data are warranted with an assessment of OS to support the evaluation of benefit-risk in patients with hematologic malignancies.

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 for discussion. Maybe I can start asking maybe an ignorant question as a drug developer myself, and if I can ask Dr. Conaway or Dr. Coffey to help me understand a bit of this.

Dr. Conaway, you mentioned earlier that there are multiple ways that you can do trial designs to address the questions that we all have and we saw today in the presentations. I think one of my concerns is censoring when you are actually doing

these clinical trials, especially single-arm studies.

What is the true effect when you have a higher dropout rate in the experimental arm, if you will, that either is related to poor drug tolerability, and therefore patients need to actually come off trial before; even if you document progression, how does censoring, or lack thereof, affect PFS and ultimately impact outcomes survival-wise?

DR. CONAWAY: My comments were really about the dose optimization phase of this, not the comparative phase, and I'll defer to others, Dr. Coffey or the FDA, for how they handle PFS and OS in the presence of censoring due to tolerability.

DR. GORMLEY: Hi. This is Nicole Gormley. I'll ask Dr. Gwise to comment.

DR. GWISE: Yes. Hi. This is Thomas Gwise, FDA. In the face of censoring that's motivated by early dropout to the toxicity, PFS could potentially be biased. In reviewing the studies that we get with PFS, we always do some sensitivity analysis to evaluate the amount of bias that could be caused by

such informative censoring.

DR. GARCIA: Thank you.

Does anybody else in the panel have any comments, questions, about what you saw with the toxicity data and how that can impact subsequent therapy, and therefore maybe even outcome?

Dr. Nieva?

DR. NIEVA: Thank you. Jorge Nieva, USC. I want to clarify that the question at hand really relates to other malignancies outside of chronic hematologic malignancies, that what we're really asking here is whether a PI3-kinase inhibitor, even if it's demonstrated to have a benefit in an area of unmet need -- let's say they were found to be highly effective for glioblastoma or some other tumor for which there is a desperate need for better therapy -- that option would be restricted, and there would not be any accelerated approvals granted in that case, and really, we're moving beyond the question of hematologic malignancy.

So I guess my question is, is the issue of whether or not there is an unmet need moot, and is

that really what you're asking? Thank you.

DR. GORMLEY: Hi. This is Nicole Gormley. Thanks. Our question here really is limited to the use of PI3-kinase inhibitors and heme [ph] malignancies. There is obviously lessons from this discussion that we will take back and think about, and how that applies to other areas within drug development, but the question to the committee here is really -- and the discussion is really -- the PI3-kinase inhibitors and whether randomized data with an assessment of OS is needed for patients with heme malignancies.

I think where we're coming from here is that we have this body of experience with these products in this class in multiple indolent lymphomas that have shown significant toxicities and concerns with dosing, and I think that has implications for future exploration of PI3-kinase inhibitors within heme malignancies.

Of course, again, yes, we will take back conversations here and apply them or think about how they may apply to other scenarios, other indolent

diseases, or PI3-kinase development in other spaces. But the question here today is, based on the experience that we have, what should we be doing with PI3-kinase inhibitors in the future in heme malignancies?

One other aspect that I want to point out is you mentioned in your question are we ruling out accelerated approval for all future development, et cetera, and just one other important point to highlight is that accelerated approval does not have to equate with single-arm trials. Accelerated approval can be based on randomized trials still using early endpoints, and that's something that we have encouraged a paradigm for with multiple sponsors; that they consider an initial, for example, randomized trial that's powered for both early efficacy endpoints such as response rate, and powered for later endpoints such as progression-free survival such that one single trial is used.

Sponsors would come in with the randomized data for accelerated approval after having met the response rate endpoint, and then both patients will

continue to be followed for overall survival or progression-free survival for regular approval once that data is available, but with a single-trial model. So the requirement, or the question asking about randomized data really is separate from the question of accelerated approval or not; so just to highlight those two things.

I think those are all the comments. I'll open it up to see if there's anyone else from the FDA that wants to comment.

(No response.)

DR. GORMLEY: Okay. Hear none. Thank you.

DR. NIEVA: Thank you. That was complete.

DR. GARCIA: Thank you.

Dr. Thanarajasingam?

DR. THANARAJASINGAM: Thanks, Dr. Garcia.

I just wanted to make some summary comments, putting all of this together from my perspective, both as a lymphoma hematologist and a researcher focused in understanding toxicity and tolerability.

My perspective here is that no one is arguing that there's not a clear efficacy signal or that

development of this drug class should be halted and they shouldn't be available to our patients. But the question is whether randomized data are warranted as a regulatory strategy here.

As a clinician, these aren't drugs that I'm reaching for initially, but they're ones that I would like to have available as options for my patients in later lines, usually after exhausting other available options. But for patients in later lines of therapy, whose life expectancy is most limited by their disease, the benefit-risk assessment is still very crucial, and it's still first do no harm for this precious population of patients.

There's a concerning pattern of results here related to PFS benefits that lead to approvals, and potential OS decrements that warrant additional scrutiny in the context of accompanying information about disproportionate toxicity and deaths in the PI3-kinase inhibitor treatment arms of several studies across the board.

There's more than one reason why PFS and OS don't track, but the most concerning of them is

treatment-related toxicity and deaths, and here the potential for harm can't be ruled out. It's interesting that efforts to gain clarity on these findings have not routinely panned out.

The required postmarketing studies to affirm initial accelerated approvals haven't always been conducted, or the drugs are being pulled from consideration, before the public and scientific community can get a clear understanding of why, in scientifically rigorous peer-reviewed publications. And there are also very legitimate concerns that we've discussed about dose optimization, so a lot there.

Although the voting question focuses on what type of trial is needed, I also, like Dr. Garcia, think that the type of endpoints we need to look at will be important. We all know that requiring OS endpoints of indolent lymphoid malignancies is impractical, and the intent is not to stifle progress and the speed to which therapies come to our patients. But sole dependence on PFS with these studies is problematic, and we really have to

consider some composite outcomes that include PFS, along with predefined safety and tolerability endpoints, which are informed by patient-reported data as well.

I feel that given the unique issues discussed today pertaining to this class of agents in further drug development, I would hope that the FDA might be able to require some of those elements, even if that's not standardly the case.

So in summary, I do think that to understand the benefit-risk ratio in patients with hematologic malignancies, randomized data, where possible, is very important. I'm very interested in hearing from my other colleagues on the panel. Thank you.

DR. GARCIA: Excellent early summary, Dr. Thanarajasingam. Fantastic. Thank you.

Let's move on with Dr. Cheng.

DR. CHENG: Thanks, Dr. Garcia. I'm Jon Cheng, the industry rep. This is actually a clarification for Dr. Gormley regarding the question.

I appreciate the question regarding randomized data. My question is regarding assessment

of overall survival as to how the FDA was thinking about assessment, particularly in situations where it's an indolent disease.

The discussion is on the assessment of it and how an assessment is done, particularly if it's not a properly powered overall survival endpoint, which often very large studies and obviously intervene treatments can complicate that, so I'm interested in a less powered overall survival data set and how an assessment is potentially interpreted.

If I may, just as a secondary, is this driven by the toxicity theme with this class, and would it be relevant to classes that maybe have a safety profile that's distinct and maybe with a less toxic profile?

DR. GORMLEY: Hi. This is Nicole Gormley. Thank you for that really good question. We've had a lot of discussion about that here in the agency, and we are in this meeting here talking about this class of products and their development in hematologic malignancies. But I think these discussions really have implications of these data for many indolent

diseases, where you can't rely on overall survival as the primary endpoint, and sometimes we may have early overall survival data.

I'd like to ask Dr. Rodriguez to speak briefly about how we're thinking about some of these overall survival assessments in going forward.

Dr. Rodriguez?

DR. RODRIGUEZ: Hi. Thank you.

We do have some considerations for future studies. Looking forward to future studies that can evaluate overall survival in randomized studies, we have some statistical points to consider. While FDA has demonstrated commitment to timely approval of safe and effective cancer treatments through the use of earlier endpoints, survival is the paramount objective for intervention.

A plan for evaluating OS should be prespecified in the protocol when designing studies, even if not conducting hypothesis testing for efficacy. A prespecified plan will be useful for a safety evaluation of OS in which potential harm to patients may be adequately ruled out based on a

prespecified data cut.

Sponsors have an obligation to demonstrate their products are safe and effective. Approaches to early assessment and interpretation of OS may be useful, such as adapting trial monitoring approaches that may include utility analyses or Bayesian prediction. These are our primary considerations at this point for future studies.

I may also summarize slide 75 again, which covered what we looked at for the PI3K inhibitor class. These were not prespecified; these were exploratory analyses. Based on a low number of events, we did have uncertainty, but we did focus on an estimated hazard ratio and confidence interval to provide descriptive information. We also looked at the death rates by treatment arms to provide important summaries.

This is the basis of the overall survival and what we were thinking about in future studies. I hope that answered the question.

DR. CHENG: It does, and thank you for that. Are there different potential thoughts based on the

toxicity profile or safety profile of an agent or class, or is this kind of universal?

DR. RODRIGUEZ: I think these are general thoughts in terms of what we're looking at when we particularly have early OS data and this exploratory analysis, where we did not have a prespecified data cut which would be a prespecified number of events, and we were not conducting hypothesis testing.

DR. CHENG: Understood. Thank you very much.

DR. GARCIA: Thank you both.

Dr. Sung?

DR. SUNG: Anthony Sung, Duke University. Just taking a step back, I feel like this discussion is different from a lot of other ODAC meetings, where we meet and we discuss the specific drugs and the safety and efficacy of a specific drug, while during this meeting a lot of data was presented on a number of PI3 kinases, which I agree are problematic.

Part of me struggles with the question at hand and implications for the class as a whole, and for future drug developments within this class. What if a new PI3 kinase is developed that has phenomenal

single-arm data? Would we still require a randomized trial in that setting?

I feel like usually when we meet, we meet on questions and we evaluate the data at hand, which I feel comfortable doing. But I feel like this question is asking us about the future, which is a little bit different. Thank you.

DR. GORMLEY: This is Nicole Gormley. And you're absolutely right; this is a very different advisory committee meeting, and it is future thinking and forward-looking. I think, though, where we're coming from is that we want to make sure that our forward-thinking advice that we give to sponsors is grounded in our experience. We want to make sure that we are learning the appropriate lessons from this experience.

I mean, in reality, this degree of safety findings that we're seeing in overall survival results across multiple products, across multiple hematologic indications, and all showing this consistent finding of concerning overall survival patterns, albeit early, is really unprecedented. So

while we definitely want to expedite drug development and make sure that there are new therapies available to patients as soon as possible, it's imperative, in our view, that we ensure that those products are safe and effective.

There are many ways that drug development can be expedited, and it doesn't all require a single-arm trial. I mentioned how randomized trials can also be used for accelerated approval, and we have lots of other mechanisms to expedite drug development and work with sponsors as well to expedite development, and then also processes and programs to expedite our review for really effective therapy.

But I think the issue that we're seeing here is that all of these products have activity, but they also have a very concerning safety profile that really has only been able to be fully characterized with the randomized data. So our question is, given, again, this unprecedented body of data that we have thus far, going forward should we require randomized data?

DR. SUNG: If I may follow up?

DR. GARCIA: Sure, go ahead.

DR. SUNG: I guess my question is -- and like I said, I agree with you on all the data of the drugs that have been presented to date and I share your concerns. But my question is, we can't predict the future, and what if in the future another drug in this class comes along that appears to have phenomenal safety data as well as a strong suggestion of efficacy even in phase 1 studies, can that go on to just a single-arm phase 2 study?

I feel like it's hard to make -- that's why I find it hard to struggle with this question because it involves the future, and we don't know what's going to happen down the line.

DR. GORMLEY: No, we definitely don't know what the future is. I will say, though, that none of us have a crystal ball, but we are also not automatons. If the cure for cancer is developed tomorrow, I think we can find ways to review this expeditiously, to study it expeditiously, et cetera. None of us have a crystal ball, but I think that it's really important that we don't make the same mistakes

from yesterday that we learned from our experience.

Dr. Pazdur?

DR. PAZDUR: This is Dr. Pazdur. Let me just jump in here. I think you're kind of reading into this question in a little more detail than we intended. Of course we would demonstrate the appropriate degree of flexibility depending upon the safety findings, as well as the efficacy findings; that's for sure. But if something similar came along where we saw, even in the early studies, a significant toxicity here, then this should raise concern for us with regards to potential impacts in overall survival.

So we're not asking you -- as we said, we realize that we do not have degrees in fortune telling here, so to speak, but given the fact of what we're seeing here -- and here again, this is an unprecedented finding that we saw in oncology here. If we saw something similar as we move forward, should we do randomized studies? And grant it, if we saw something that had phenomenal response rates and that was very non-toxic, then that's a different

story here, and we always would demonstrate the appropriate degree of flexibility in this.

DR. SUNG: That's something that I agree with. It's just not how the question is stated.

DR. PAZDUR: Duly noted, ok?

DR. GARCIA: Thank you all.

Next, Dr. Coffey?

DR. COFFEY: Yes. I just have, I guess, a clarifying question, where I'm having trouble reconciling a couple of the comments that have come up in the discussion, where it's been mentioned multiple times in randomized trials, you can still do accelerated approval. But the emphasis on overall survival, it was referenced several times in the discussion the wide confidence intervals that you have, even in the existing data, and with the approaches that were mentioned with a futility analysis or some type of Bayesian prediction to stop, you're still going to need a decent number of events to do that.

So it seems like if that's the direction that future trials are going, that is almost, by

definition, pushing you away from accelerated approval because you're going to need longer studies before you would do that. I guess I'm trying to reconcile those two statements in my head, and just wonder if anyone might want to comment on that.

DR. GARCIA: If I may interject, we're close to time, and we have still a voting question. So I would ask the group, whoever is left answering questions or comments, to keep them brief and succinct, please.

DR. GORMLEY: Yes. This is Nicole.

I'm sorry. Could you clarify your question again? Is it the distinction about the randomized data versus -- could you just clarify your question again?

DR. COFFEY: My question was more, the plans for future trials with overall survival and randomized, if you're using futility roles or Bayesian prediction to have stopping rules, that's going to take a number of events. With the wide confidence intervals that you report in the studies that have been done, it would be hard to have

reasonable stopping rules in those, which seems to push it away from the option of accelerated approval that has been mentioned numerous times and is still on the table.

So it almost seems, by definition, if you go in that approach, the accelerated approval is going to be a much harder pathway just because the numbers aren't going to be there. So I'm trying to reconcile how could you do that type --

DR. PAZDUR: Not necessarily. Obviously, you would take a look at an accelerated approval, for example, on a response rate, which would require fewer numbers of patients and an overall survival analysis or even a time to progression analysis -- this is Dr. Pazdur -- but you actually have the trial ongoing, so you could actually see these effects later on.

Rather than doing these trials sequentially, a randomized trial versus this continuation of a randomized trial in one trial, one actually has the trial ongoing. So we're not saying that we would hold up an accelerated approval necessarily for a

survival analysis, but they would be forthcoming relatively rapidly -- one would hope -- certainly not a year or two years later, that's for sure, or many years later.

DR. COFFEY: Thanks. That clarifies it.

DR. PAZDUR: Here again, the truth of accelerated approval is basically to try to shorten the period of time between the designation of accelerated approval and basically the confirmation of clinical benefit or lack of confirmation of clinical benefit.

This single-study approach where we have an accelerated approval on a response rate in earlier clinical endpoint is one that we're really advocating. Then you do have the trial ongoing, so there's none of this issue of, well, it's going to take us several years even to get a randomized trial ongoing in a specific disease, and then you have drugs out there that potentially are harming people with a long period of time on the market. That's what our interest is here.

Clear?

DR. GARCIA: Thank you, Dr. Pazdur.

We have one final comment.

Dr. Diehl?

(No response.)

DR. GARCIA: Dr. Diehl, you may be muted still.

DR. DIEHL: Can you define the word "warranted" in question 1? For example, does it mean the defining factor is overall survival, or it will be considered, or it should be pre-planned? What does the word mean, "warranted"?

DR. GORMLEY: Yes. This is Nicole Gormley. The "warranted" was, again, referring to the randomized data. Randomized data are warranted, and it should include an assessment of overall survival. We are not suggesting that overall survival be the primary endpoint.

Again, as stated earlier, what we're really after, or asking here, is should we have randomized data for initial approval? And again, accelerated approval can still be used with a response rate, but with a randomized trial, and those trials followed

for overall survival; then, again, as mentioned earlier, initial looks, early looks, interim futility analyses for overall survival, as well, throughout the trial.

But the amount of information available from randomized data is so much more robust, including patient-informed outcomes; a better assessment of safety and attribution of the toxicity observed; tolerability, et cetera, across the board from randomized data as compared to single-arm trials.

So given the experience that we've seen thus far, none of these trials evaluated overall survival as the primary endpoint, and that's not what we're suggesting. The question, or the discussion point, is, should randomized data be required for initial approval, and with some looks or assessments of overall survival with that trial?

DR. DIEHL: Thank you.

DR. GARCIA: Thank you.

Before we move on to question 2, which is a voting question, let me just briefly summarize what the panel has reviewed.

It does appear that the efficacy signal does exist. We think that these agents do provide efficacy. The biggest issue, obviously, is tolerability, based upon the data that we have seen throughout all these class of agents. The benefit and risk assessment remains critical for drug development in this context, certainly for patients who have a prolonged natural history and certainly in the context of second- and third-line therapy as well.

There were also some comments that the patterns for the hazard ratios for survival are concerning, including deaths; the frequent withdrawal of agents, that appeared to be concerns that are legitimate as well; and finally, perhaps the need for us as a group and drug developers in the country to innovate with new endpoints, and certainly include PROs in all these clinical trials.

Perhaps for me, there is no doubt that patients want timely access to new cancer therapies, but certainly they have to expect that us as investigators identify those therapies that offer

real benefits in their lifetime.

We move on to the next question. This is a voting question. Given the observed toxicities with this class, previous randomized trials with a potential detriment in OS, and a narrow range between effective and toxic doses, should future approvals of PI3-kinase inhibitors be supported by randomized data?

Dr. She-Chia Chen will provide instructions for the voting.

DR. S. CHEN: Hi. This is She-Chia Chen. 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 discussions 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 from the screen into the record. Hereafter, the chairperson will go down the roster and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to.

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

(No response.)

DR. GARCIA: I'm going to read the question again. Given the observed toxicities with this

class, previous randomized trials with a potential detriment in overall survival, and a narrow range between effective and toxic doses, should future approvals of PI3-kinase inhibitors be supported by randomized data?

Are there any questions about the wording of the question?

(No response.)

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

DR. SUNG: Sorry. This is the Anthony Sung from Duke. I just raised my hand.

Dr. Pazdur, should we vote on the question as it's written or on the sense of the question as you had previously articulated?

DR. PAZDUR: Well, the issue here, I think they're not inconsistent here. We're just asking should randomized studies be done here. We're not asking for overall survival to be the primary endpoint of the trial, but a randomized trial does allow us to at least do a descriptive analysis of

that endpoint. That cannot be obtained from a single-arm trial. So I view this question as totally consistent with my previous comment.

DR. SUNG: I guess in my mind, the inconsistency is previously you had said if there is phase 1 data that raises some concerns, then we should do a randomized study, which --

(Crosstalk.)

DR. PAZDUR: Here again, we would have the flexibility here. I think it's well worded here, "given the observed toxicities." This was a toxic regimen. We had potential detriments in overall survival here, so in general, would people support a randomized study?

Obviously, there are exceptions to anything, and we would demonstrate the appropriate flexibility, depending on what we saw in these earlier studies here. But given the class of drugs here, if you had to do a development plan over, I think most people would agree -- and not to lead the committee here -- that there should have been randomized studies here, obviously, done earlier.

DR. SUNG: And I absolutely agree with these drugs that have been presented, but if a future drug does not show toxicity in phase 1 studies --

DR. S. CHEN: This is the DFO, She-Chia. Just a friendly reminder, please vote as the question is --

DR. GARCIA: Yes, as the way it is. We can --

(Crosstalk.)

DR. S. CHEN: -- and we can go ahead and move on. Thank you so much.

I'll pass it to you, Dr. Garcia.

DR. GARCIA: There is an opportunity after you vote for you to state and comment as to why you voted, so please save those comments for after your vote, if you will. Just vote as the question reads.

DR. ADVANI: I have a quick question. Are we voting on the randomized trials of two different doses?

DR. GARCIA: The question to me is clear, so I would suggest for you to vote based upon what the question states, and then you can actually think as

to why you voted the way that you voted after, and make comments regarding that after you vote.

Dr. Chen, do you want to take us to --

DR. S. CHEN: Great. Thank you.

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 results display, I will read the vote results into the record.

(Pause.)

DR. S. CHEN: The vote results are displayed. I will read the vote totals into the record. There are a total of 16 yeses, zero nos, and 1 abstention.

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 the reason why you voted as you did, if you want to.

DR. GARCIA: Thank you.

We will now go down the list and have everyone who voted to state their name and vote into

the record. You may also provide justification for your vote, if you wish to. We will start with Dr. Chen.

Andy?

DR. A. CHEN: Andy Chen. I voted yes.

DR. GARCIA: Thank you.

Dr. Sung?

DR. SUNG: Anthony Sung. I abstained for partly the reasons that we had already discussed, but to summarize here, I agree that the drugs that have been evaluated in this class and discussed today are highly problematic, and how those evaluations were done has its faults, and randomized studies should have been done in that context.

However, I still feel uncomfortable labeling an entire class and requiring further future drugs in that class to be supported by randomized data. I think if the phase 1 data is concerning, then, absolutely, a randomized study should be needed. If the phase 1 data is not concerning, then I don't know if randomized studies should be needed in that case. Thank you.

DR. GARCIA: Thank you.

Dr. Coffey?

DR. COFFEY: Yes. Chris Coffey. Yes.

DR. GARCIA: Dr. Lieu?

DR. LIEU: This is Chris Lieu. I voted yes. I think when you look at the significant concern that overall survival endpoints were indolent cancers, this can be costly, extremely time-consuming, and I think that the utilization of PFS benefit as an endpoint for regulatory approval is potentially more reasonable with therapies of limited toxicity. In this case, I think it's likely not reasonable in a situation where therapies have significant toxicities.

Also, agents with significant toxicities may lead to the potential confounders to progression-free survival, as has been brought up during the course of this call. And also with the available data, you at least hope to see at least a trend towards overall survival, even with subsequent lines of therapy confounding that. But with this class of agents, in some trials the reverse actually appears to be true,

further highlighting the concerns that are raised today.

The bottom line is if we aren't improving length of life with any therapy but exposing patients to toxicity, and therefore decreasing their quality of life, are we truly helping our patients? And I don't believe so. This concludes my comments. Thank you.

DR. GARCIA: Thank you.

Mr. Mitchell?

MR. MITCHELL: Yes. I'm David Mitchell. I voted yes. I think we need randomized trials to ensure that the products we're addressing today are safe and effective, and don't do harm.

DR. GARCIA: Thank you.

Dr. Thanarajasingam?

DR. THANARAJASINGAM: This is Gita Thanarajasingam. I voted yes, and I don't have anything to add to my prior summary comments.

DR. GARCIA: Thank you.

Dr. Au?

DR. AU: I'm Jessie Au. I voted yes.

DR. GARCIA: Thank you. Jorge Garcia. I voted yes. Multiple points.

I fully believe, and it's perplexing to me, the lack of appropriate doses, [indiscernible] studies for these agents, especially when they're using combination or existing regimens for those diseases. Certainly, the AE profile and the reduction in dose and drug discontinuation, as presented by the group, is quite perplexing to me as well, and quite toxic in my mind.

Also, the trends of survival detriment, it is something, again, that is perplexing to me, and the reality of it is -- I think, clinically, even though I'm not a hematologist myself -- I could probably find it quite difficult to tell a patient that I have an agent that could reduce your tumor volume, possibly delay your progression, but at the price of significant toxicities. And by the way, I can also impact your mortality in a detrimental manner.

Dr. Nieva?

DR. NIEVA: It's Jorge Nieva from USC. I voted yes. Randomized data are always ideal to show

efficacy and safety. Single-arm data is valuable for approval of novel agents and in areas of unmet need. The question, as worded, is specific to PI3-kinase inhibitors for chronic hematologic malignancies. Well, we now have lots of agents on the market, so there is no unmet need where approval based on a single-arm study would have been sufficient.

The current safety data justify raising the bar for new agents in the class to show that they are not causing long-term harm. I am concerned, however, that the selection of study endpoints may have impacted toxicity, and indolent lymphoproliferative disorders in particular, it should be noted that the PFS may have biased drug design for longer term drug administration rather than fixed-dose administration, and this long-term administration for these drugs may have been detrimental to patients. Response rate may have been a preferable endpoint in these disorders, and there should be attention to endpoints that reflect clinical benefit with shorter term administration. Thank you.

DR. GARCIA: Thank you.

Dr. Dunleavy?

DR. DUNLEAVY: Hi. Kieron Dunleavy. I voted yes. I have no further comments to add to my previous comments.

DR. GARCIA: Thank you.

Dr. Diehl?

DR. DIEHL: Lou Diehl. The speakers made a compelling case, and the solution that they proposed, a randomized trial, go a long way towards solving the problem. Thank you.

DR. GARCIA: Thank you.

Dr. Conaway?

DR. CONAWAY: Mark Conaway. I voted yes. I think the results presented provide ample evidence that randomized trials should be part of the approval process for PI3K inhibitors. I think they also highlight the need for improvements in the design, conduct, and reporting of the dose exploration trials, leading up to the randomized trial.

DR. GARCIA: Thank you.

Dr. Cristofanilli?

DR. CRISTOFANILLI: Yes. Massimo

Cristofanilli. I voted yes. I think it's very clear from the studies that there is a class effect toxicity that we need to keep in mind for the future with regard to dose-finding studies, and a randomized study is the only way to address acute and chronic toxicity to see if these drugs have a future in hematological malignancy.

DR. GARCIA: Thank you.

Ms. Nadeem-Baker?

MS. NADEEM-BAKER: This is Michele Nadeem-Baker. I vote yes for the reasons already stated by Dr. Lieu. And although I don't want to stand in the way of progress with drugs, the evidence presented is very compelling that this class of drugs needs to be supported by randomized data. Thank you.

DR. GARCIA: Thank you.

Dr. Advani?

DR. ADVANI: I voted yes for the reasons already stated by my colleagues on this call, and I was reassured by Dr. Pazdur's comment about having flexibility in case the next agent in this class of drugs come along, which has amazing activity, that

there might be some flexibility. Thank you.

DR. GARCIA: Thank you.

Dr. Madan?

DR. MADAN: Yes. This is Ravi Madan. I voted yes. I think the historical experience here really begs for randomized data. I think our patients have an expectation not just to live longer, but to live as long as they can to maintain the quality of life, and randomized data will provide confidence for physicians and patients alike, provide that.

DR. GARCIA: Thank you.

Dr. Kraft?

DR. KRAFT: This is Walter Kraft, and my vote is yes. The well-established power and benefits of randomization and evidence generation strongly outweigh disadvantages of this approach in the case of PI3K inhibitors and in the current therapeutic landscape. Thank you.

DR. GARCIA: Thank you all.

Again, just to summarize, we have 16 yes and 1 abstain. Pretty much everybody who voted yes is

talking about the standard for clinical trial designs to be randomized trials, the concerns of survival detriment, the benefit-risk ratio in that patient population with long natural history, and the importance of quality of life as you prolong life for these patients. Certainly, PFS, at least for most of us who voted yes, didn't appear to be an original endpoint for this class of agents.

For the person who abstained, the concerns were simple and related to labeling a class of agents that in the future may pan out to be effective and safe for most patients.

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

DR. GORMLEY: This is Nicole Gormley. Thank you all for your comments. They're very insightful, and thank you for your time.

Adjournment

DR. GARCIA: Thank you.

I would like to thank the FDA for an excellent presentation, the committee members for an active session of questions and a robust discussion

despite some questions about the questions at hand, and certainly the FDA and ODAC staff for making this meeting possible.

We will now adjourn the meeting. Thank you all, and stay safe.

(Whereupon, at 3:45 p.m., the meeting was adjourned.)