FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Virtual Meeting

Thursday, March 9, 2023

12:00 p.m. to 5:24 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

She-Chia Jankowski, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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Professor

Division of Translational Research and

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Scientist Chair

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(11:00 a.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 Lauren-Jei McCarthy. Her email and phone number are currently displayed.

My name is Jorge Garcia, and I will be chairing today's meeting. I will now call the last session of the March 9, 2023 meeting of the Oncology Drug Advisory Committee to order. Dr. She-Chia Jankowski is the designated federal officer for this meeting, and she will begin with introductions.

Introduction of Committee

Dr. Jankowski?

DR. JANKOWSKI: Thank you, Dr. Garcia.

Good afternoon. My name is She-Chia Jankowski, and I am the designated federal officer for this meeting. When I call your name, please

introduce yourself by stating your name and affiliation.

We'll first start with ODAC members.

Dr. Conaway?

DR. CONAWAY: Yes. Good morning. Mark Conaway, biostatistics, University of Virginia.

DR. JANKOWSKI: Dr. Garcia?

DR. GARCIA: Good morning. Jorge Garcia, GU medical oncologist and the division chair for Solid Tumor Oncology at University Hospitals Seidman Cancer Center, Case Western Reserve University in Cleveland, Ohio.

DR. JANKOWSKI: Dr. Madan?

DR. MADAN: Good morning. My name is Ravi Madan. I'm a medical oncologist at the National Cancer Institute with primary research focused on prostate cancer.

DR. JANKOWSKI: Dr. Sung?

DR. SUNG: Anthony Sung, associate professor of medicine, Division of Hematologic Malignancies and Cellular Therapy, Duke University.

DR. JANKOWSKI: Dr. Vasan?

DR. VASAN: Good morning. I'm Neil Vasan. I'm a breast oncologist and physician scientist at Herbert Irving Comprehensive Cancer Center at Columbia University Medical Center in New York City.

DR. JANKOWSKI: And Dr. Cheng?

DR. CHENG: Hello. Jon Cheng, also a medical oncologist, and I'm the industry rep, and I work for Bristol-Myers Squibb.

DR. JANKOWSKI: Next are our temporary voting members.

Dr. Coffey?

DR. COFFEY: Hi. I'm Chris Coffey. I'm a biostatistician at the University of Iowa.

DR. JANKOWSKI: Dr. Diehl?

DR. DIEHL: Lou Diehl, Duke University, Division of Hematologic Malignancies and Cell Therapy.

DR. JANKOWSKI: Dr. Dunleavy?

DR. DUNLEAVY: Hi. I'm Kieron Dunleavy. I'm the director of oncology at Lombardi Comprehensive Cancer Center and professor of

medicine at Georgetown University, Washington, D.C.

DR. JANKOWSKI: Dr. Finestone?

DR. FINESTONE: Yes. Sandra Finestone, consumer representative.

DR. JANKOWSKI: Mr. Majkowski?

MR. MAJKOWSKI: I'm Paul Majkowski from New York, lymphoma survivor, serving as the patient representative.

DR. JANKOWSKI: Dr. Nowakowski?

DR. NOWAKOWSKI: Greg Nowakowski. I'm a medical oncologist specializing in lymphoma at Mayo Clinic Rochester, where I also serve as the deputy director of the Cancer Center for Clinical Research.

DR. JANKOWSKI: Dr. Pai?

DR. PAI: Good afternoon. Amit Pai, professor of clinical pharmacy, University of Michigan, Ann Arbor.

DR. JANKOWSKI: And Dr. Sekeres?

DR. SEKERES: Good afternoon, everyone. I'm Mikkael Sekeres, chief of hematology and professor of medicine at the Sylvester Comprehensive Cancer

Center, University of Miami, and also former chair of ODAC.

DR. JANKOWSKI: Finally, we have FDA participants.

Dr. Pazdur?

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

DR. JANKOWSKI: Dr. Theoret?

DR. THEORET: Hi. Mark Theoret, deputy director of Oncology Center of Excellence, FDA.

DR. JANKOWSKI: Dr. Gormley?

(No responses.)

DR. JANKOWSKI: Dr. Gormley, I think you're on mute.

DR. GORMLEY: Hi. Can you hear me now? This is Dr. Nicole Gormley, division director, Division of Hem Malignancies II at the FDA.

DR. JANKOWSKI: Thank you.

Dr. Kasamon?

DR. KASAMON: Hi. This is Yvette Kasamon, clinical team leader, Division of Hematologic Malignancies II at the FDA.

DR. JANKOWSKI: And Dr. Yazdy?

DR. YAZDY: Hi. I'm Maryam Yazdy. I'm a hematologist/oncologist and clinical reviewer at the lymphoma team in the Division of Hematologic Malignancies II.

DR. JANKOWSKI: Thank you.

Dr. Garcia?

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 topics during the break. Thank you.

Dr. Jankowski now will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. JANKOWSKI: 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 the discussion on supplemental biologics license application, BLA, 761121/S-008, for Polivy, polatuzumab vedotin-piiq, for injection, submitted by Genentech, Inc. The proposed indication, use, for this product is in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone, for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma, DLBCL.

This product was approved under 21 CFR 601.41, subpart E, accelerated approval regulations, for use in combination with bendamustine and a rituximab product for the

treatment of adult patients with relapsed or refractory DLBCL, not otherwise specified, after at least two prior therapies.

Confirmatory studies are postmarketing studies to verify and describe the clinical benefit of a product after it receives accelerated approval. The new proposed indication is based on the confirmatory study, POLARIX, Study GO39942, conducted to fulfill postmarketing requirement 3630-1 detailed in the June 10, 2019 approval letter, available at www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/761121Orig1s000ltr.pdf.

Based on the results of the POLARIX study, the committee will discuss the benefit-risk profile of Polivy in patients with previously untreated DLBCL. This is a particular matters meeting during which specific matters related to Genentech's sBLA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict

of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

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

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

to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. GARCIA: Thank you, Dr. Jankowski.

We will now proceed with the FDA introductory comments from Dr. Yvette Kasamon.

Dr. Kasamon?

FDA Introductory Comments - Yvette Kasamon

DR. KASAMON: Good afternoon. I'm Yvette Kasamon, a hematologist/oncologist and clinical team leader in FDA's Division of Hematologic Malignancies II. I will provide a brief introduction to the polatuzumab vedotin application and the issues under discussion.

The applicant is seeking traditional approval of polatuzumab vedotin as part of first-line therapy for diffuse large B-cell lymphoma. Polatuzumab vedotin was granted accelerated approval in 2019 for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma not otherwise specified after at least two prior therapies.

Polatuzumab vedotin is a CD79b directed antibody drug conjugate. CD79b is a component of the B-cell receptor expressed on most mature B cells, including most cases of diffuse large B-cell lymphoma. Polatuzumab vedotin contains a humanized antibody against CD79b conjugated to the anti-mitotic agent MMAE.

Accelerated approval of polatuzumab vedotin was based on complete remission rate and duration of response in a randomized phase 2 trial, comparing polatuzumab vedotin plus bendamustine/rituximab versus bendamustine/ rituximab alone in 80 patients with relapsed or refractory diffuse large B-cell lymphoma.

With the accelerated approval of polatuzumab vedotin, a postmarketing requirement was issued for a confirmatory trial in the frontline setting for diffuse large B-cell lymphoma. This confirmatory trial, POLARIX, is the topic of this meeting. POLARIX is a randomized, double-blind, placebo-controlled trial of polatuzumab vedotin plus R-CHP; that is rituximab, cyclophosphamide,

doxorubicin, and prednisone versus R-CHOP in patients with untreated large B-cell lymphoma, with a primary endpoint of progression-free survival.

Before discussing the issues with POLARIX, I'd like to briefly review the evidentiary criteria for FDA approval. Drugs granted accelerated approval or traditional approval must meet the same statutory requirements for safety and effectiveness for safety. For safety, there must be sufficient information to determine that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling.

For effectiveness, there must be substantial evidence of effectiveness based on adequate and well-controlled investigations that allow for the conclusion that the drug will have the effect that it is represented to have in the proposed labeling. For a single randomized trial to support an application, results must be sufficiently robust and compelling.

I am reviewing these criteria because the applicant seeks an indication for polatuzumab

vedotin for patients with previously untreated diffuse large B-cell lymphoma, a potentially curable disease based on a single randomized trial. We are seeking the committee's input on whether the data from POLARIX supports a clinically meaningful and persuasive treatment effect in this potentially curative setting.

As the applicant is seeking a first-line indication for diffuse large B-cell lymphoma, I'd like to take a moment to briefly review the treatment landscape. R-CHOP has been the long-standing U.S. standard and can cure approximately 60 percent of all cases of newly diagnosed diffuse large B-cell lymphoma. Rituximab is the only FDA-approved product for first-line diffuse large B-cell lymphoma in almost two decades. The approval was supported by three randomized-controlled trials, each demonstrating a statistically significant overall survival advantage with the addition of rituximab. Multiple randomized-controlled trials have attempted, but failed, to improve upon the R-CHOP regimen, most

often involving add-on design.

I will next review the design of POLARIX. The FDA is convening this ODAC meeting to discuss issues arising from POLARIX, a randomized-controlled trial that attempted to improve upon R-CHOP. Based on these results, the applicant seeks approval of polatuzumab vedotin in combination with R-CHP for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma. POLARIX is a randomized, double-blind, placebo-controlled trial that evaluated the substitution of vincristine with polatuzumab vedotin in the R-CHOP regimen in adults with previously untreated large B-cell lymphoma. The treatments are outlined here.

This was a superiority substitution trial comparing pola+R-CHP to R-CHOP in 879 adults with untreated large B-cell lymphoma with an International Prognostic Index of 2 or greater. Each treatment arm also received a placebo for either vincristine or polatuzumab vedotin. Dosing of the other drugs was the same in both arms. The

primary endpoint was progression-free survival assessed by investigators. The key secondary endpoints were a modified event-free survival endpoint, complete remission rate at the end of therapy, and overall survival.

I'd like to clarify the study population because there are aspects of this population that we will highlight. Please note that the applicant's references to diffuse large B-cell lymphoma include high-grade B-cell lymphoma and other large B-cell lymphomas. High-grade B-cell lymphomas, which were also included in POLARIX, are very aggressive lymphomas, divided into high-grade B-cell lymphoma with MYC/BCL2 and/or BCL6 translocations, also referred to as double-hit or triple-hit lymphoma, and high-grade B-cell lymphoma not otherwise specified. Please note that more intensive regimens than R-CHOP are generally preferred in the U.S. for high-grade B-cell lymphoma due to concerns for higher treatment failure with CHOP-type regimens.

I will next summarize the major topics for

discussion. There are a number of important considerations regarding the results of POLARIX that warrant a public discussion. The first topic I will highlight today is the modest progression-free survival benefit of pola+R-CHP compared to R-CHOP. This slide summarizes the applicant's primary analysis of progression-free survival or PFS. Although the difference in PFS was statistically significant in this analysis, the effect size with polatuzumab vedotin was modest, with an estimated 4.1 percent absolute improvement at 1 year and an estimated 6.5 percent absolute improvement at two years.

The FDA performed various sensitivity analyses to evaluate the robustness of the treatment effect. Regardless of the sensitivity analysis and censoring rules, the PFS differences were modest, and the largest calculated absolute improvement at two years in the pola+R-CHP arm was 6.5 percent.

Of note, in the CHOP regimen, the specific contribution of vincristine is unknown, as the

efficacy of CHOP versus CHP has not been directly compared. Because POLARIX was a substitution trial, substituting polatuzumab vedotin for vincristine, there are challenges in understanding the contribution of polatuzumab vedotin to the overall regimen.

I will next summarize the overall survival results. This slide shows the Kaplan-Meier plot of the final analysis of overall survival with a median follow-up of 3.3 years. In this superiority trial, the curves were similar with no demonstrated improvement in overall survival in the pola+R-CHP arm. At some landmark time point, the overall survival rates were either similar or numerically lower in the pola+R-CHP arm.

Overall survival is an important metric of both safety and efficacy. POLARIX was not adequately powered to detect improvement in overall survival, and there is uncertainty due to the low event rate. Subsequent therapy may also impact the observed overall survival results; however, a trial need not be powered for overall survival to provide

important information, and the FDA relies on the overall survival analysis, even if descriptive, to inform the benefit-risk determination.

Next, I will summarize outcomes of other efficacy endpoints. CR rate at the end of therapy, as determined by blinded independent central review, was a prespecified endpoint in POLARIX with alpha allocation. The results were not statistically significant, and there was little difference, about 4 percent, in the observed CR rates. Thus, the observed improvement in progression-free survival is not explained by a statistically significant improvement in the depth of response.

Other prespecified secondary endpoints showed modest differences. Modified event-free survival, also referred to as PFS efficacy, was an alpha allocated secondary endpoint and was statistically significantly greater in the pola+R-CHP arm. However, the treatment effect was modest. The one-year point estimates differed by 3.8 percent with a confidence interval that

included zero. The two-year point estimates differed by 6.2 percent.

The applicant's analyses of duration of response and disease-free survival also suggested modest benefits with pola+R-CHP; however, these are not intention-to-treat based analyses or controlled for type 1 error, so are considered exploratory.

The next topic for discussion is the heterogeneity of the study population. I would like to highlight the lymphoma subtypes in the POLARIX trial and the differences in outcome. The predominant type of lymphoma in POLARIX was diffuse large B-cell lymphoma not otherwise specified, with the minority of patients having high-grade B-cell lymphoma or other large B-cell lymphoma.

This slide shows progression-free survival and overall survival by lymphoma subgroups. The purpose of this subgroup analysis is to explore the consistency of the treatment effect across the population without any formal comparison. We can see that the treatment effect appears to be heterogeneous across lymphoma subgroups.

The treatment effect also appears heterogeneous with respect to CR rate at the end of therapy. We acknowledge that these are exploratory post hoc evaluations with sample size limitations. Because diffuse large B-cell lymphoma not otherwise specified is the most common type of non-Hodgkin's lymphoma in the U.S. and comprise most of the trial populations, I would like to highlight the outcomes in this subgroup.

In patients with diffuse large B-cell lymphoma not otherwise specified, the PFS hazard ratio was 0.75, the CR rates by treatment arm were similar, and the overall survival hazard ratio was 1.02. An important aspect of this discussion is the overall survival results in this subgroup, which I will detail in the next slide.

This slide shows the final overall survival analysis in the DLBCL NOS subgroup, representing 740 patients or 84 percent of the trial population. The overall survival hazard ratio was 1.02 with an upper bound of 1.49. The 1-year overall survival estimates were 91.8 percent in the pola+R-CHP arm

versus 95.5 percent in the R-CHOP arm.

While there is uncertainty associated with the point estimates due to low event rates, we find these outcomes concerning. The overall survival outcomes are of utmost importance, given the patient population we are discussing today; namely, patients with previously untreated diffuse large B-cell lymphoma being treated with curative intent.

I'd like to mention the safety outcomes. This slide shows a brief summary of selective safety findings in POLARIX. In general, the safety findings were comparable between arms, including rates of peripheral neuropathy. Fewer patients had recovery of peripheral neuropathy in the polatuzumab arm. A few adverse events occurred more often in the polatuzumab arm, including febrile neutropenia, infection, nausea, and diarrhea. The reported incidences of neutropenia were similar but likely underestimated based on the schedule of lab evaluations.

In summary, the outcomes of POLARIX raise a number of important topics for discussion. These

include the modest improvement in the primary outcome measure of progression-free survival, lack of improvement in overall survival, and the uncertain impact on overall survival due to the limited number of events, and lack of improvement in CR rate. Results of other prespecified secondary endpoints were modest and had limitations.

Additionally, the heterogeneity of the study population and observed treatment effect may impact the generalizability of the findings. In the largest subgroup, that is diffuse large B-cell lymphoma not otherwise specified, again, the hazard ratio for overall survival exceeded 1 with an upper bound of 1.49.

The applicant seeks a frontline indication on the basis of this single large randomized trial; however, these findings create uncertainty about the benefit-risk profile of pola+R-CHP in patients with previously untreated large B-cell lymphoma, a setting where, again, treatment is delivered with curative intent. Ultimately, it is incumbent upon

the applicant to provide robust evidence to the FDA to support that the drug is safe and effective in the intended population.

I will now present the discussion topics for the committee. As a first topic, please discuss the benefit-risk profile of pola+R-CHP for the proposed patient population with large B-cell lymphoma, including patients with diffuse large B-cell lymphoma not otherwise specified, considering the results of the POLARIX trial. Also, based on the results of the POLARIX trial, specifically the overall survival results, please discuss whether additional follow-up data from POLARIX should be required to inform the benefit-risk of polatuzumab vedotin in patients with large B-cell lymphoma in the frontline setting.

Following these questions, we will ask that the committee vote on the following question. Given the results of the POLARIX trial, does polatuzumab vedotin have a favorable benefit-risk in patients with previously untreated large B-cell

lymphoma, including diffuse large B-cell lymphoma not otherwise specified. This concludes my presentation. Thank you for your attention.

DR. GARCIA: Thank you, Dr. Kasamon.

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

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

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

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

We will now proceed with the presentations from Genentech, Inc.

Applicant Presentation - Charles Fuchs

DR. FUCHS: Good morning, and good afternoon. I'm Dr. Charles Fuchs, senior vice president and global head of Oncology and Hematology Product Development at Genentech and Roche. I want to thank Dr. Garcia, the committee members, Dr. Pazdur, and the FDA staff for this opportunity to discuss our supplemental biologics license application for polatuzumab vedotin in combination with rituximab plus cyclophosphamide, doxorubicin, and prednisone, or pola+R-CHP for the treatment of patients with previously untreated diffuse large B-cell lymphoma.

My background is as a medical oncologist. I previously worked at the Dana-Farber Cancer Institute, and subsequently served as director of

the Yale Cancer Center. In 2021, I had the privilege of joining Genentech and Roche to lead oncology and hematology drug development.

Today I'm joined by Dr. Christopher Flowers, ad interim head of cancer medicine and chair of lymphoma and myeloma at the University of Texas, MD Anderson Cancer Center; Dr. Jonathan Friedberg, Samuel Durand professor and director at the Wilmot Cancer Institute at the University of Rochester. Dr. Flowers and Dr. Friedberg both served as investigators and steering committee members for the POLARIX trial.

I'm also joined by my colleagues at Genentech and Roche, Dr. Jamie Hirata, global development leader for the polatuzumab vedotin program; Dr. Imola Fodor, vice president and global head of Hematology, Data, and Statistical Sciences; and Dr. Calvin Lee, senior medical director and medical monitor of the POLARIX study.

Our agenda today following my introduction will include Dr. Flowers will offer up the background and unmet need for patients with diffuse

large B-cell lymphoma; Dr. Hirata will offer the efficacy and safety data for the POLARIX trial; Dr. Friedberg will offer clinical perspectives in light of these data; and then I will offer closing remarks.

For more than 20 years, rituximab in combination with the CHOP chemotherapy regimen, or R-CHOP, has been the mainstay of first-line therapy for diffuse large B-cell lymphoma, and while 60 percent of patients are cured by R-CHOP, 40 percent have disease refractory to treatment or will relapse after an initial response. For those 40 percent of patients with relapsed/refractory disease, more effective salvage therapies have emerged, including CAR-T therapy and stem cell transplant. However, these second- or later-line therapies offer a much lower chance for cure and much greater treatment-related toxicity. As such, developing a first-line treatment more effective than R-CHOP represents an important unmet medical need.

As we'll discuss today, the POLARIX trial is

the first study in over 20 years to show improved benefit-risk over R-CHOP for first-line DLBCL patients. Patients treated with polatuzumab vedotin plus R-CHP, or pola+R-CHP, experienced a clinically meaningful and statistically significant 27 percent reduction in the risk of progression, relapse, or death when compared to those treated with R-CHOP. Importantly, the safety profile of pola+R-CHP is comparable to that of R-CHOP. Based on these data, we believe that pola+R-CHP offers meaningful benefit without adding risk, and the best chance for cure for patients in the first-line treatment of diffuse large B-cell lymphoma.

Polatuzumab vedotin is an antibody drug conjugate that targets CD79b, a component of the B-cell receptor signaling complex that is ubiquitously expressed on B lymphocytes. As you've heard, the antibody is linked to MMAE, a highly potent microtubule inhibitor currently used in multiple FDA-approved antibody drug conjugates.

In 2019, FDA granted accelerated approval for polatuzumab vedotin, also known as Polivy, in

combination with bendamustine and rituximab, for the treatment of relapsed/refractory diffuse large B-cell lymphoma. At the time of accelerated approval, confirmation of clinical benefit was required by one of either two ongoing phase 3 studies, the POLARIX trial and first-line therapy, which we'll be discussing today, or the POLARGO trial in the second or later line of therapy relapsed/refractory disease. POLARIX is the sponsor's earliest opportunity to fulfill the postmarketing commitment to confirm clinical benefit.

POLARIX was designed to test the hypothesis that replacing vincristine in R-CHOP with polatuzumab vedotin provides for targeted delivery of a high level of a more potent microtubule inhibitor, MMAE, thereby increasing efficacy while limiting the systemic release of unconjugated MMAE, thereby minimizing additional toxicity.

In the briefing document, there are a number of points of agreement between the sponsor and the FDA. Specifically, both parties acknowledge that

POLARIX met its primary endpoint with a statistically significant improvement in progression-free survival, and that the overall safety profile for pola+R-CHP was comparable to R-CHOP. Nonetheless, the agency submits that the improvement in PFS demonstrated in POLARIX was modest, and there is a lack of benefit in overall survival.

As you'll hear from Drs. Flowers and Friedberg, the PFS status as demonstrated in the POLARIX trial is clinically meaningful in the first-line treatment of DLBCL. More effective first-line therapy spares the patients the needs of the toxicities and burden of salvage therapy and provides patients with a single greatest chance for cure and a life free of cancer.

The FDA's review of POLARIX also includes analyses of treatment effect by locally determined histopathological subtype. While POLARIX is a large, robust phase 3 trial, the study was not designed nor powered to study treatment effect by local pathologic subtype. Of note, as you will

hear from our doctors, for each subtype in the specific classification used, R-CHOP remains an accepted standard of care. No less importantly, CD79b, the target of polatuzumab vedotin, is ubiquitously expressed across each of these subtypes.

To be clear, we are all committed to interrogating the POLARIX database as thoroughly as possible to fully characterize the study's findings. That said, we recognize that these and other post hoc subset analyses are exploratory and hypothesis generating.

I now turn to Dr. Flowers to offer additional context of diffuse large B-cell lymphoma and the unmet need in first-line therapy.

Dr. Flowers?

Applicant Presentation - Christopher Flowers

DR. FLOWERS: Thank you, Dr. Fuchs.

I'm Dr. Christopher Flowers, professor and chair of the Department of Lymphoma and Myeloma at the University of Texas MD Anderson Cancer Center, and it's a great privilege to describe the disease

background and unmet need for patients with diffuse large B-cell lymphoma.

Diffuse large B-cell lymphoma is the most common blood cancer in the United States, with more than 27,000 people diagnosed each year. Routine diagnosis of large B-cell lymphoma and diffuse large B-cell lymphoma can be made by a hematopathologist. Currently, the term "large B-cell lymphoma" is used more commonly because diagnoses are more commonly made using a core needle biopsy, where a diffuse growth pattern may not be able to be seen. This is reasonable because both large B-cell lymphoma and diffuse large B-cell lymphoma have the same treatment. Diffuse large B-cell lymphoma is aggressive and typically presents with advanced stage disease, and uniformly requires treatment at diagnosis.

As has been described, diffuse large B-cell lymphoma is a heterogeneous disease and includes a number of ways to define subtypes, as shown on this slide. Unlike general diagnosis, accurate subtyping requires the input of academic expert

pathologists, and there can be disagreement among experts. In fact, in 2022, two different classification systems were proposed by international panels of experts, making consistent subtyping even less reliable. The bottom line is that there is no evidence for benefit for any therapy over R-CHOP in any subtype from previous randomized-controlled trials, including the use of more intensive regimens.

Although applying biological subtypes has been less useful for addressing unmet needs for diffuse large B-cell lymphoma, clinical factors have been robustly validated to determine prognosis. The International Prognostic Index, or IPI, has been a standard clinical tool used for risk stratification. The IPI includes age; ECOG performance status; lactate dehydrogenase, or LDH, a laboratory value; the number of extranodal sites where lymphoma is involved; and the Ann Arbor stage of lymphoma as risk factors.

Each risk factor adds one point to the total IPI score. The graph to the right shows the

progression-free survival curves by IPI score for patients treated in first-line randomized-controlled trials with R-CHOP. As you can see in the blue, orange, and red lines, higher IPI scores represent the patients with the higher unmet need.

It is also important to note that R-CHOP is a treatment regimen that is very commonly used in all practices. Academic and community providers are very comfortable with this outpatient regimen. In the trial shown by the FDA at the beginning of the meeting with R-CHOP, neutropenia ranged from 38 percent to 58 percent. Even with neutropenia, febrile neutropenia occurred less commonly in 9 to 15 percent of patients, and high-grade infections like pneumonia occurred in 2.6 to 6 percent of patients. These studies also show that support with growth factors, or G-CSF, are commonly used with R-CHOP in studies.

Next, I'd like to take you through the treatment journey for a patient with large B-cell lymphoma. In medical oncology, there are few situations where patients with advanced stage

disease can experience cure. Large B-cell lymphoma is one of the few advanced stage cancers that can be cured with first-line treatment; however, only a portion of patients can be cured, and the difference between patients cured in the first line and those without cure is drastic. Let me walk you through the journey of a patient after a diagnosis of diffuse large B-cell lymphoma.

First-line therapy is given to patients with curative intent and can involve ancillary therapies that are given like methotrexate prophylaxis to prevent central nervous system disease spread. Radiation therapy can also be given to involve sites of disease, but remains complementary since large B-cell lymphoma is a systemic disease that requires systemic therapy. We know that first-line therapy can potentially produce progression-free periods, meaning avoidance of relapse, progression, or death.

This is the definition of progression-free survival. The vast majority of disease progression for diffuse large B-cell lymphoma occur within

2 years of diagnosis, and patients who remain on this path after 2 years represent the cured population. However, with R-CHOP, approximately 40 percent of patients fall off his path. Their journey is more challenging.

Select patients may be eligible to receive curative options in the second line such as chimeric antigen receptor T-cell therapy, or CAR-T cell therapy, stem cell transplantation, but they both require access to specialized centers. These treatments have substantial toxicity and often require prolonged hospitalization. Importantly, cure rates with these second-line treatments are much lower than they are in the first line. Among all second-line patients, CAR-T cell cures approximately 20 percent of patients; stem cell transplant cures approximately 5 percent of patients. These low rates are based on historical transplant studies and data from phase 3 CAR-T cell trials presented in a 2022 management algorithm by Drs. Sehn and Westin in Blood.

Beyond these treatments, other therapies are

available but are not considered curative. This patient journey illustrates that progression-free survival is clinically meaningful and the most useful endpoint for measuring treatment benefit in first-line diffuse large B-cell lymphoma. Ultimately, sustained progression-free survival and cure following first-line treatment is the outcome all oncologists hope for and certainly the outcome all patients are eager to receive. As an investigator and a clinician taking care of patients with lymphoma, progression-free survival incorporates the conditions required for cure and what is most important to patients: avoiding disease relapse, progression, and death.

Next, I would like to discuss how to determine the clinical benefit in first-line diffuse large B-cell lymphoma. We know that overall survival is an important and reliable endpoint for cancer. As the FDA pointed out in the briefing document and in introductory remarks, overall survival was demonstrated in trials that ultimately resulted in adding rituximab to a CHOP

over 20 years ago; however, none of those studies address the entire population of diffuse large B-cell lymphoma, two studies that only involved patients over the age of 60 and one study involved patients under age 18 to 60. But the big question is, is overall survival still a relevant endpoint in this setting?

In analysis involving international experts in lymphoma, and including 13 randomized-controlled trials in first-line diffuse large B-cell lymphoma, we collected individual patient-level data on more than 7,500 patients and showed that overall survival as an endpoint for trials in first-line diffuse large B-cell lymphoma would require more than 10 years of follow-up. In my view, this is an unacceptably long time to wait to determine whether a new therapy benefits patients.

With that said, progression-free survival of an endpoint measures and reflects what is meaningful for patients. In the past 20 years, first-line, randomized-controlled trials for diffuse large B-cell lymphoma that have tried to

improve upon R-CHOP have targeted a clinically meaningful progression-free survival hazard ratio of at least 0.75.

So how do I explain this to patients considering a clinical trial? I tell them that a hazard ratio of 0.75 really means a 25 percent reduction in the risk of progression, relapse, or death, and that translates into an absolute improvement of 5 to 7 percent in progression-free survival at the 24-month time point. The importance of the 2-year mark, or 24-month time point, is shown on the next slide.

This is another analysis of more than 5,800 patients treated on first-line, randomized-controlled trials with diffuse large B-cell lymphoma. Patients who were progression-free at 24 months, or who progressed within 24 months, are shown to illustrate the importance of this milestone. We call this PFS24. This provides a clear way of seeing the importance and magnitude of progression-free survival.

On the left, the Y-axis is the fraction of

people alive and the X-axis is the number of years after PFS24. In this curve, these patients who were progression-free at 24 months, shown in blue, are highly likely to have a similar life expectancy to those of sex- and age-matched controls shown in the dotted orange line. On the right, you can see that patients who had progression before 24 months after their R-CHOP regimen, shown in blue, had markedly worse survival after progression than age- and sex-matched controls.

In addition to impact on survival, progression is a devastating event for patients and families who are hoping for cure. The implications include symptoms related to the disease, the B-symptoms, the fevers, night sweats, and weight loss, and pain associated with the sites where the lymphoma is involved. Although subsequent therapies can be administered as I described, those are associated with lower cure rates, hospitalization, and can have late effects.

The centers that provide curative second-line therapy can also be many hours away, a

major barrier for ill patients. Collectively, these challenges can lead to loss of productivity and diminish quality of life with second or later lines of therapy.

In summary, when we think about treatment of large B-cell lymphoma, first-line therapy offers the best chance of cure. With R-CHOP as the only FDA-approved therapy, there remains an unmet need to reduce relapse and progression for first-line patients. Sustained progression-free survival best represents cure, and for this reason, PFS is a clinically meaningful endpoint for first-line diffuse large B-cell lymphoma, and prior designs of trials support that a hazard ratio of 0.75 or better is an indicator of clinical benefit. This amounts to a 5 to 7 percent improvement in PFS at 2 years.

At MD Anderson, we see approximately 500 newly diagnosed patients with large B-cell lymphoma each year. An improvement of 2-year progression-free survival by 5 to 7 percent would mean that 25 to 35 of those patients might avoid

relapse disease and the need for subsequent treatment.

Based on my understanding of the disease and the data that you will hear next from Dr. Hirata, I believe that the POLARIX trial meets the criteria for providing a clinically meaningful benefit for patients, and I recommend that patients with large B-cell lymphoma, in regions where health authorities or guidelines allow it, receive pola+R-CHP to improve their likelihood of progression-free survival and cure. I thank you for your attention, and we'll turn to Dr. Hirata to describe the results of the POLARIX trial.

Applicant Presentation - Jamie Hirata

DR. HIRATA: Thank you, Dr. Flowers.

To address the unmet medical needs that exist in the first-line setting of DLBCL that Dr. Flowers described, we designed and conducted the phase 3 POLARIX trial that replaces vincristine with polatuzumab vedotin in the R-CHOP regimen with the goal of improving outcomes for these patients. Today I'll go over the POLARIX data with you. My

name is Jamie Hirata, and I am the global development leader of the polatuzumab vedotin program.

POLARIX is a phase 3 ongoing study, evaluating the combination of polatuzumab vedotin with R-CHP versus R-CHOP in patients with DLBCL. This is a randomized, double-blinded active and placebo-controlled trial. It is multiregional and enrolled patients from across 22 countries, where sites in the United States recruited the most patients. POLARIX is being conducted in collaboration with the French Lymphoma Study Association and a steering committee that includes global lymphoma experts.

Patients were eligible for enrollment if they had previously untreated DLBCL and were between the ages of 18 to 80 with an IPI score of 2 to 5. This represents patients currently with the highest unmet need in the first-line setting. 879 patients were randomized to either one of two treatment arms and were stratified by IPI score, bulky disease status, and geographic region.

Patients could receive R-CHOP plus a polatuzumab vedotin placebo or polatuzumab vedotin at 1.8 milligrams per kilogram plus R-CHP, plus a vincristine placebo. Both regimens were given every 21 days for 6 cycles, and patients in both treatment arms received two additional cycles of rituximab monotherapy.

The key study endpoints in hierarchical testing order are displayed here. The primary endpoint of the study was progression-free survival, which is defined as the time from randomization to progression, relapse, or death. The secondary endpoint of event-free survival for efficacy, or PFS efficacy, was tested next. The definition of this endpoint counts events that include biopsy confirmed residual disease or subsequent treatment.

In addition to PFS events just described, this endpoint was designed in collaboration with FDA to reflect PFS events that are due to efficacy reasons. The two other key secondary endpoints were overall survival and complete response at the

end of treatment, assessed by a blinded independent central review. If PFS efficacy was positive, then alpha would be split between these two endpoints.

In the POLARIX statistical analysis plan, we prespecified that the primary analysis would be conducted on the intention-to-treat population after two conditions were met. The first is that the sample size required 228 events to demonstrate 80 percent power with two-sided alpha, 0.05; and second, that all patients were followed for at least 24 months, the time point that Dr. Flowers discussed as important.

At the clinical cutoff date in June of 2021, with a minimum 24 months and median follow-up of 28.2 months, we observed 241 PFS events. Prior to unblinding, we incorporated all of the recommendations, including analysis, methodologies, and all censoring rules for PFS.

Here are the patient demographics and baseline characteristics. You can see they were balanced between the two arms, in particular by age and IPI score. Importantly, the patients enrolled

in POLARIX were representative of patients with DLBCL in the first-line setting who received R-CHOP.

Now let's review the efficacy data. POLARIX met its primary endpoint, demonstrating a statistically significant and a clinically meaningful improvement of progression-free survival with pola+R-CHP compared to R-CHOP. A hazard ratio of 0.73 was observed with a statistically significant p-value of 0.0177. The observed hazard ratio translated to a 27 percent reduction in the relative risk of disease progression, relapse, or death with pola+R-CHP compared to R-CHOP.

Additionally, there was a 6.5 percent improvement in 2-year PFS for treatment with pola+R-CHP that resulted in a higher proportion of patients who are progression-free at 2 years. As Dr. Flowers discussed, the 2-year milestone is meaningful, as patients who are progression-free would be highly likely to have a similar life expectancy as those in a sex- and age-matched general population.

Here is the Kaplan-Meier curve for progression-free survival showing the results from the primary analysis. You can see there is a separation in the curves that demonstrate the clinically meaningful improvement in progression-free survival with R-CHP, shown in green, relative to R-CHOP, shown in blue. On the right are results from an additional year of follow-up.

Here, you can see that the initial clinical benefit is durable and persist with a further improvement at the 3-year milestone of 7.7 percent. This provides additional evidence that the 2-year PFS time point is stable as mean events are not accumulating.

To fully understand the treatment effect of pola+R-CHP compared to R-CHOP, we assessed the impact of subsequent therapy. Subsequent therapies can be administered prior to or after disease progression, and I'll go over these clinical decision points that would warrant an additional treatment for patients with DLBCL. With this in mind, I'll discuss how three different PFS analyses

were performed.

In POLARIX, non-protocol anti-lymphoma therapy, or NALT, is defined as any subsequent anti-lymphoma therapy that is different from the prescribed protocol treatment of either R-CHOP or pola+R-CHP. In clinical practice, subsequent anti-lymphoma therapy can be given to patients before disease progression for two main reasons. First, as Dr. Flowers mentioned, patients felt to have a high risk of CNS involvement may receive high-dose methotrexate, and patients with bulky or extranodal regions may receive radiotherapy as concomitant therapy in order to maximize cure as part of their first-line treatment. These therapies would be unlikely to change response to DLBCL treatment.

In the second scenario, if residual disease is still present, most patients would receive additional therapy as a second attempt to achieve a response for this aggressive disease. If disease progression occurs, a change in therapy would also be necessary. The need for any additional therapy

for the presence of residual disease and/or progression reflects unfavorable outcomes for these patients.

Now let's go through how we accounted for subsequent therapies in the primary, sensitivity, and post hoc PFS analyses. The primary PFS analysis and PFS sensitivity analysis were prespecified in the statistical analysis plan. The primary PFS analysis, as shown in the table, did not apply censoring for subsequent therapy administered prior to progression, given that these decisions were made in a double-blinded manner. This follows the intention-to-treat principal and answers the clinical question, will pola+R-CHP prolong the time to progression and death, regardless of the need for subsequent therapy?

One preplanned sensitivity analysis censored for subsequent therapy, excluding preplanned radiotherapy, as depicted in yellow in the table. This analysis revealed an imbalance in the censoring prior to observed PFS events, with more than twice the number of patients censored in the

R-CHOP arm than in the pola+R-CHP arm despite double-blinding. This imbalance led to further interrogation.

After the primary readout, we worked and aligned with the FDA to determine rules that identified which scenarios of subsequent therapies to censor. This is depicted in yellow in the third row of the table, where the censored therapies are limited to additional therapy needed for the presence of residual disease prior to a progression and exclude CNS prophylaxis and preplanned radiotherapy.

A post hoc PFS analysis was then conducted that applied the agreed-upon censoring rules and allows us to assess the impact on PFS. In this table, you can see the results of the post hoc analysis. The hazard ratio of 0.74 in the third row is consistent with the primary PFS result, with the hazard ratio of 0.73 in the first row. All three PFS analyses account for subsequent therapies in different ways and are consistent and ultimately support the primary PFS results.

A key secondary endpoint is PFS for efficacy. Instead of accounting for subsequent therapies by censoring for them in the PFS analyses that I just walked you through, PFS efficacy incorporates subsequent therapies given to patients for efficacy reasons and the presence of residual disease as events. This is important because as we've mentioned previously, avoiding the need of any subsequent therapy for any reason in the first-line treatment setting is a clinically meaningful outcome.

Here you can see the Kaplan-Meier curve showing the superior benefit of PFS efficacy in the pola+R-CHP arm in green compared to R-CHOP in blue. The PFS hazard ratio is 0.75, a statistically significant result consistent with PFS.

In POLARIX, three statistically evaluated overall survival analyses were performed as shown in the table on the left. There were two interim analyses and one final analysis. At each overall survival analysis, there continues to be a low event-to-patient ratio observed, and at the final

analysis, approximately 15 percent of events have occurred in each arm. In other words, most study patients are alive to date. Furthermore, post-treatment safety signals are not detected.

The final overall survival Kaplan-Meier curve is shown on the right. With approximately 3 years of follow-up, there was no significant [inaudible] difference in overall survival. Importantly, the hazard ratio remained below 1 at each time point.

One of the concerns identified by the FDA was a slight separation favoring R-CHOP in the 8-to-18 month period in the overall survival Kaplan-Meier curve at the primary analysis, acknowledging that early overall survival may be an important indicator of both efficacy and safety outcomes. To address the FDA's concerns, we reviewed the survival data rigorously. After examination of all deaths that occurred in the first 18 months, neither the agency or the sponsor found a safety signal.

As Dr. Flowers outlined, overall survival

requires a long follow-up in the first-line setting; therefore other secondary endpoints take on greater importance to supplement the PFS observation as evidence of a meaningful clinical benefit.

Complete response is an important objective of therapy. As shown in the bar graph, while not statistically significant, the end of treatment complete response rate for R-CHOP was 74 percent and 78 percent for pola+R-CHP. Despite not seeing a significant difference in response rates between the treatment arms, we did see prolonged durability of responses with pola+R-CHP compared to R-CHOP. Disease-free survival on the left and duration of response on the right were prespecified endpoints, and although these endpoints were not included in the hierarchical testing, they should be considered relevant, as durability is a more important outcome than response alone for patients.

In the POLARIX trial, the majority of patients are responders in both treatment arms. For patients who achieved a complete response after

receiving pola+R-CHP, a more durable response is demonstrated by an improvement in disease-free survival compared to R-CHOP. Similarly, there was a longer duration of response in patients who achieved partial or a complete response as their best overall response with pola+R-CHP compared to R-CHOP. The remissions achieved with pola+R-CHP were more sustained, showing a quantitative difference between responders in treatment between the treatment arms.

As discussed, preventing relapse and avoiding subsequent therapies are very meaningful for patients. In addition to an improvement in progression-free survival, patients in the pola+R-CHP arm required less subsequent anti-lymphoma therapy for either efficacy or safety reasons than in the R-CHOP arm. As you can see, fewer patients needed subsequent radiotherapy and systemic therapies with pola+R-CHP, and of the systemic therapies received, fewer patients received stem cell transplants and CAR-T cell therapy in the pola+R-CHP arm.

In this double-blind active and placebo-controlled trial, we observed that the overall safety profile of pola+R-CHP is comparable to R-CHOP. Now, let's discuss some of the key safety results.

This bar graph shows the breakdown of the overall safety profile. There were approximately 60 percent of grade 3 or 4 adverse events observed across both arms. The incidence of grade 5 or fatal adverse events were comparable with 2.3 percent with R-CHOP and 3 percent with pola+R-CHP. These rates are similar to that observed in other randomized phase 3 trials that evaluated R-CHOP in the first-line setting. For serious adverse events, rates were also similar between the treatment arms. When it comes to treatment modification, the pola+R-CHP arm had comparable incidence of treatment discontinuation and dose interruptions to the R-CHOP arm, and there were less dose reductions that occurred in the pola+R-CHP arm. In the first-line treatment of DLBCL, maintaining intensity of therapy is

predictive of positive curative outcomes. In POLARIX, the relative dose intensity was high for both arms, indicating that pola+R-CHP was as well tolerated as R-CHOP.

Here are the most common adverse events observed in the trial. Neutropenia, febrile neutropenia, and peripheral neuropathy are adverse events of particular interest, and I'll expand on these in subsequent slides. As mentioned, rates of any grade and grade 3 or 4 adverse events were similar between the arms, with a couple of exceptions that I'll point out. There were 5 percent and 10 percent more patients in the pola+R-CHP arm that experienced all-grade nausea and diarrhea, respectively. These adverse events did not impact treatment delivery and were resolved after treatment.

As you heard from Dr. Flowers, hematologic toxicities are well recognized adverse events associated with R-CHOP therapy, and the clinical management of these adverse events are well understood within the lymphoma community. Now I'll

focus in on neutropenia, febrile neutropenia, and infections, as these are adverse events of important consideration.

G-CSF prophylaxis was used in the management of neutropenia. Use was high in both treatment arms, where 93.2 percent of patients in the R-CHOP arm and 90.1 percent in the pola+R-CHP arm received G-CSF prophylaxis. The incidence of all-grade neutropenia was generally comparable, and grade 3 or 4 neutropenia was observed in 40.2 percent with R-CHOP versus 41.8 percent with pola+R-CHP. Serious neutropenic events were higher in the pola+R-CHP arm mainly due to a higher incidence of serious febrile neutropenia. When looking at the overall rates of febrile neutropenia, they were higher with pola+R-CHP, 14.3 percent, versus 8 percent with R-CHOP. As Dr. Flowers mentioned, this rate is in line with that observed in other phase 3 trials that evaluated R-CHOP. Importantly, in POLARIX, febrile neutropenia was not observed after completion of chemotherapy with cycle 6 in both arms.

In terms of dose deliverability, the higher incidence of neutropenia did not impact this, as study treatment discontinuations, dose reductions, and dose interruptions were comparable. And last, at the clinical cutoff date, 99.1 percent of all neutropenia, including febrile neutropenia, had resolved.

As a consequence of neutropenia, there is a concern about infection. In the POLARIX trial, the proportion of patients who experienced infections in the pola+R-CHP arm was higher than in the R-CHOP arm, 49.7 percent versus 42.7 percent, respectively. The incidence of grade 3 or 4 and serious infections were also numerically higher in the pola+R-CHP arm. Of note, fatal infections or grade 5 events were similar between the arms, with 1.4 percent occurring with R-CHOP and 1.1 percent with pola+R-CHP. The increased incidence of infections in the pola+R-CHP arm did not lead to an increase in study treatment discontinuations or dose reductions compared with R-CHOP, and treatment interruptions were comparable. At the time of the

clinical cutoff, the majority of patients in both treatment arms reported that all infections had resolved.

Peripheral neuropathy is an adverse event of particular interest for microtubule inhibitors such as vincristine and polatuzumab vedotin. The proportion of patients who experienced neuropathy was comparable between arms, where the majority of the events were grade 1. Patients treated with pola+R-CHP experienced fewer dose discontinuations and dose reduction due to neuropathy, and overall, the majority of patients reported that neuropathy events had resolved 56.9 percent in R-CHOP and 57.8 percent in the pola+R-CHP arm. Of note, because the onset of neuropathy was earlier for vincristine as compared to polatuzumab vedotin, the resolution of neuropathy occurs marginally earlier among patients who received R-CHOP.

Health-related quality of life was measured in POLARIX. Of note, the scales only collected information before disease progression or relapse. Here I'm showing one of the patient-reported

outcome measures, representing global quality of life as measured by the EORTC QLQ-C30 tool. The line graph shows that all patients in both treatment arms experienced improvements in the global scales of quality of life while on treatment and after treatment. In addition, these improvements in quality of life were comparable in patients from both treatment groups.

I'd like to conclude by summarizing the results of the POLARIX trial. First, unimportantly, POLARIX is a positive study and met its primary endpoint of progression-free survival. A more durable progression-free survival was observed with pola+R-CHP and had a higher proportion of patients that were progression free at 2 years. Both aspects are meaningful for patients.

Second, pola+R-CHP and R-CHOP have a comparable overall safety profile as demonstrated in the double-blind, placebo-controlled trials. The POLARIX efficacy and safety results together demonstrate a positive benefit-risk with pola+R-CHP

as first-line treatment for patients with diffuse large B-cell lymphoma.

Thank you for your attention and for this opportunity to share the POLARIX data. Now I'd like to invite Dr. Friedberg to share his clinical perspective.

Applicant Presentation - Jonathan Friedberg

DR. FRIEDBERG: Thank you, Dr. Hirata.

I'm Jonathan Friedberg, director of Wilmot Cancer Institute at University of Rochester. I have cared for patients with lymphoma for over 25 years. I'm an independently funded clinical investigator and currently serve as chair of the SWOG Lymphoma Committee and a member of the Lymphoma Steering Committee for the NCI National Clinical Trials Network. I've received no consulting fees and have no financial relationships with Genentech, the sponsor.

As you've heard from Dr. Flowers, diffuse large B-cell lymphoma remains one of the few advanced stage cancers curable with medical therapy. I think it is therefore essential that we

viewed the discussion and decision today through this lens. PFS means something very different in a disease like diffuse large B-cell lymphoma compared to the metastatic solid tumor setting, since in lymphoma it equates to cure.

Despite marked improvements in our understanding of the biology and heterogeneity of diffuse large B-cell lymphoma, the standard therapeutic approach for most patients, R-CHOP, has not changed in the past 20 years. More than 12 large randomized trials have been conducted over that time frame. All of them used R-CHOP as the comparator arm. These studies all used PFS as the primary endpoint, they all targeted similar hazard ratios, and had similar sample sizes.

The POLARIX trial was a large study by lymphoma standards, robustly conducted, and included a placebo control. This is the first positive trial in this space since the original rituximab results were published in 2002. Primary results of POLARIX, as you've just seen, showed improved progression-free survival at 2 years for

patients receiving pola+R-CHP compared to R-CHOP, with a similar toxicity profile.

The vast majority of relapse events in diffuse large B-cell lymphoma occur in the first 2 years after initial treatment, which gives credence to the 2-year time point. But I think most importantly, subsequent follow-up of the POLARIX trial confirms this; that between year 2 and year 3, there were only 26 lymphoma progressions observed out of 879 patients, or a 2.9 percent event rate, and there were numerically more progressions in the R-CHOP arm compared to the pola+R-CHP arm in this time frame. So, to me, this clearly demonstrates the PFS superiority over R-CHOP and the durability of the pola+R-CHP regimen.

There are a few situations in oncology, or indeed all of medicine, where we would withhold curative therapy. Relevant particularly to the lymphoma field, brentuximab vedotin was approved in combination with EBV chemotherapy by the FDA in 2018 for patients with advanced stage Hodgkin

lymphoma, which is another curable disease, based upon a single randomized trial, ECHELON-1, that showed only a 5 percent improvement in PFS compared with the historical standard, ABVD. As a result of that trial, BV-AVD is now the consensus standard of care for patients in that setting.

So speaking as a physician on behalf of my patients, the ultimate goal in treating diffuse large B-cell lymphoma, like Hodgkin lymphoma, is to maximize the cure rate and avoid salvage approaches that are toxic, expensive, and achieve only moderate success. The pola+R-CHP regimen clearly accomplishes this, and I stand with the NCCN Guidelines Committee and other international experts in calling for the approval of this curative regimen for the upfront treatment of diffuse large B-cell lymphoma.

I'll now turn it back to Dr. Fuchs.

Applicant Presentation - Charles Fuchs

DR. FUCHS: Dr. Friedberg, thank you for those perspectives.

As a career gastrointestinal oncologist,

I've worked in a framework where both progression-free and overall survival have been the principal endpoints to assess efficacy in the first-line treatment of patients with advanced disease. However, in contrast to most advanced solid tumor malignancies, first-line therapy for DLBCL has potential to cure more than half of all patients. Moreover, while far less curative than first-line treatment and far more toxic, second and later line therapies for DLBCL, such as CAR-T and stem cell transplant, allow patients to live much longer with relapsed disease.

As we heard from Dr. Flowers, in the current era of DLBCL treatment, trials designed to test overall survival as an endpoint would require more than a decade of follow-up. Clearly, we seek to deliver new and improved outcomes to patients faster than every 10 or more years. As such, in today's treatment landscape, overall survival is no longer a practical endpoint in the first-line treatment of DLBCL. Nonetheless, it is critical that all first-line trials document that no

detriment in overall survival is observed.

In their topics for discussion, the FDA asks whether additional follow-up of overall survival should be required. As you heard, 2- and 3-year follow-up in the POLARIX trial consistently show there is indeed no detriment in overall survival for patients treated with pola+R-CHP. We will, of course, continue rigorous follow-up for overall survival in POLARIX and will certainly share those updated results with health authorities, investigators, and the lymphoma community.

As Drs. Flowers and Friedberg, shared in the setting of first-line therapy of DLBCL, progression-free survival is a clinically meaningful validated and established endpoint. Moreover, the magnitude of benefit in progression-free survival is documented by the POLARIX trial -- 6 and a half percent at 2 years. 7.7 percent at 3 years -- is clinically meaningful. A 6.5 percent improvement in 2-year progression-free survival could prevent progression or relapsing over a thousand patients in the U.S.

annually, eliminating the need for toxic less curable therapy and, importantly, delivering to those patients the greatest chance for a life free of lymphoma.

On the basis of the POLARIX trial, polatuzumab vedotin, in combination with pola+R-CHP, has received approval for the first-line treatment of diffuse large B-cell lymphoma in 61 countries, including the European Union, the United Kingdom, Canada, Japan, and China. More recently, in the United States, the National Comprehensive Cancer Center Network, or NCCN, designated pola+R-CHP as a category 1 preferred treatment recommendation for the first-line treatment of patients with diffuse large B-cell lymphoma.

Many of us in this meeting know there are few events more devastating in the life of a patient than hearing the news that the cancer is back. My colleagues and I are here today to ensure that DLBCL patients in the U.S. have access to more effective first-line therapy that offers the

greatest chance of cure and a life free of cancer.

Pola+R-CHP delivers a magnitude of reduction in disease progression and relapse that is clinically meaningful to patients, confronting a new diagnosis of DLBCL, avoiding the need for salvage therapies that are toxic and far less likely to deliver cure. Moreover, as stipulated by both the sponsor and the FDA, the overall safety profile of pola+R-CHP was comparable to R-CHOP.

We therefore believe that the favorable benefit-risk profile demonstrated by the POLARIX study supports regular FDA approval of pola+R-CHP as a first-line treatment for diffuse large B-cell lymphoma patients in the United States. We thank you for the opportunity to present these data. This concludes our presentation. We turn back to Dr. Garcia and the committee, and we look forward to answering your questions.

DR. GARCIA: Thank you, Dr. Fuchs, and thank you to all the Genentech presenters.

We will now proceed with the FDA presentation from Dr. Maryam Yazdy.

FDA Presentation - Maryam Yazdy

DR. YAZDY: Good afternoon. I am Maryam Yazdy, a hematologist/oncologist in the Division of Hematologic Malignancies II at the FDA. I will present the FDA's discussion on the benefit-risk of polatuzumab vedotin based on the POLARIX trial results in patients with untreated large B-cell lymphoma. The members of the FDA review team are listed here. My presentation represents their collective input.

The FDA discussion for today's ODAC will start with a summary of the regulatory background and disease setting. The main topics under discussion include the modest progression-free survival benefit of polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin, and prednisone or pola+R-CHP. The overall survival results and other efficacy endpoints such as complete response rate, modified event-free survival, duration of response, and disease-free survival, and finally the heterogeneity of the study population. This will be followed by other

topics, including safety, dosing, and patient-reported outcomes.

The applicant has proposed the following indication. Polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone, or R-CHP, is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma. The proposed dose is 1.8 milligram per kg IV every 21 days for 6 cycles. I would like to point out that the applicant's definition of diffuse large B-cell lymphoma is broad and includes other histologies such as high-grade B-cell lymphoma.

Polatuzumab vedotin was granted accelerated approval in 2019 for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma not otherwise specified after at least two prior therapies. The recommended dosage was 1.8 milligram per kg IV every 21 days for 6 cycles.

The efficacy of pola to support the accelerated approval was based on IRC-assessed

CR rate, and duration of response in Study GO29365, a randomized, open-label trial of 80 patients with relapsed/refractory diffuse large B-cell lymphoma assigned to receive pola plus bendamustine and rituximab or BR alone. The efficacy results are shown in the table.

For products granted accelerated approval, for post-approval trials, verified anticipated clinical benefit may be required. At the time of accelerated approval, two postmarketing requirements were issued to verify clinical benefit. The first was POLARIX, a randomized, double-blind, placebo-controlled trial of pola+R-CHP versus R-CHOP in previously untreated diffuse large B-cell lymphoma with a primary endpoint of PFS. The second confirmatory trial was POLARGO, a randomized open-label trial of pola plus rituximab, gemcitabine, and oxaliplatin versus GemOx in patients with relapsed/refractory diffuse large B-cell lymphoma. The primary endpoint is overall survival. Preliminary results are expected in late 2024. Verification of clinical benefit

through either PMR could be adequate to fulfill the accelerated approval requirement.

To provide a background on the current treatment landscape of patients with previously untreated diffuse large B-cell lymphoma, I would like to take a step back and present a brief history of how CHOP was established as a standard of care for diffuse large B-cell lymphoma.

Multi-agent chemotherapy for diffuse large B-cell lymphoma was pioneered in 1975. Several randomized and non-randomized trials attempted to improve on the results. In 1976, a randomized-controlled trial investigated the combination of doxorubicin, vincristine, and prednisone, or HOP, versus CHOP, but added cyclophosphamide and demonstrated an overall response rate of 88 percent and 92 percent for these regimens, respectively.

A series of intensified second and third generation regimens, as shown in the table, were developed the 1980s with the goal of improving response rates mostly by adding more cytotoxic

agents and not evaluating the contribution of effect of individual drugs. In 1986, a prospective randomized safety trial was conducted to compare the relative efficacy of CHOP and several third generation combination chemotherapy regimens in patients with aggressive non-Hodgkin lymphoma.

In this trial, no significant difference in CR rate or overall survival rate was found among regimens, but toxicities were lower with CHOP. This landmark trial established CHOP as the standard-of-care regimen for diffuse large B-cell lymphoma. One aspect of this history that is important for today's discussion is that the specific contribution of vincristine for the CHOP regimen is unknown.

This slide shows you the history of the only approval in front-line diffuse large B-cell lymphoma in the last two decades, which is rituximab. In 2006, rituximab was approved in combination with CHOP for treatment of patients with previously untreated diffuse large B-cell lymphoma. This approval was based on three large

randomized trials, which included a collective enrollment of 1,854 patients with diffuse large B-cell lymphoma. Compared to rituximab, additional rituximab to first-line chemotherapy increased overall survival in each of these trials with an absolute improvement in 2-year overall survival of 9 to 11 percent.

Over the past decade, there have been numerous attempts to improve R-CHOP by modifying the regimen or adding new agents. But as you see with the examples listed in the table, these trials did not show improvement over R-CHOP alone. Additionally, some resulted in more toxicity compared to R-CHOP.

The POLARIX trial was also designed to improve upon R-CHOP by substituting vincristine with pola. POLARIX is a multicenter, randomized, double-blind, placebo-controlled substitution trial comparing the efficacy and safety of pola+R-CHP to R-CHOP in 879 adult patients with untreated large B-cell lymphoma. Patients had an international prognostic score of 2 to 5, which identified

patients with low-intermediate to high-risk disease.

The histologies in POLARIX included diffuse large B-cell lymphoma NOS, high-grade B-cell lymphoma, and other large B-cell lymphomas as listed on the slide. 440 patients were randomized to receive pola 1.8 milligram per kg plus R-CHP and a vincristine placebo for 6 cycles. 439 were randomized to receive R-CHOP plus a pola placebo. In both arms, patients received 2 cycles of rituximab afterwards.

The primary endpoint was progression-free survival assessed by investigators per Lugano 2014 criteria, and key secondary endpoints were modified event-free survival, also referred to as EFS efficacy by investigator, CR rate, and overall survival. Of note, no crossover was allowed.

This table shows the specific treatments in the POLARIX trial. As mentioned, this is a substitution trial, and the only difference between treatments was substitution of vincristine with polatuzumab vedotin in the pola+R-CHP arm. Both

regimens were the same with regards to other drugs and dosages.

Given that we are discussing a combination regimen, I'd like to share a few regulatory considerations regarding trial design. The FDA approves specific drugs and biologics based on the understanding of the treatment effect of the particular product, and while we may include in the indication that these products are approved in combination with other products, it is not the regimen that is approved.

Generally, efficacy can be demonstrated using either a superiority design, as done in POLARIX, or a noninferiority design. A noninferiority design would not have been possible for the POLARIX trial given the lack of understanding of vincristine activity and challenges associated with using a PFS endpoint for assessment of noninferiority.

With a superiority active control trial, the aim is to show superiority of the investigational agent relative to the control. A superiority

substitution trial is similar to an active control trial and aims to show superiority relative to the control; however, this can be more challenging to interpret, as a trial is conducted in combination with other agents with their own safety and efficacy profile.

In POLARIX, we have R-CHP plus pola versus R-CHP plus vincristine. Specifically in the POLARIX trial, designed as a superiority substitution trial, it is challenging to assess the contribution of effects of pola because the activity of vincristine is unknown in the setting of rituximab, cyclophosphamide, doxorubicin, and prednisone.

Before discussing the efficacy results of the POLARIX trial, I would like to clarify the diffuse large B-cell lymphoma study population. The table shows the inclusion criteria per protocol, which includes diffuse large B-cell lymphoma NOS, but also high-grade B-cell lymphoma NOS and double-hit/triple-hit lymphomas, and other large B-cell lymphomas. The FDA presentation will

use the categories as denoted on the right in blue.

Given the heterogeneity of the histology enrolled in the POLARIX trial, there are some important considerations; 84 to 85 percent of the patients had diffuse large B-cell lymphoma NOS, followed by 10 to 11 percent, who had high-grade B-cell lymphoma, including double hit or triple hit. The inclusion of high-grade B-cell lymphoma in this trial is notable because there is uncertainty whether use of R-CHOP-based therapy in patients with high-grade B-cell lymphoma is generalizable or applicable to a U.S. population.

In the U.S., these patients generally receive more intensive treatments because of poor outcomes with R-CHOP. Additionally, these patients are at higher risk of CNS involvement, yet the POLARIX trial excluded patients with active CNS disease. Taken together, this can further reduce the applicability of the trial findings for the general U.S. population with high-grade B-cell lymphoma. There are some aspects related to this concern that we will discuss more later in the

presentation.

The evaluation of the efficacy endpoints and the planned testing hierarchy and alpha allocation is shown in the figure. The primary endpoint of PFS was tested first at a two-sided alpha of 0.05. If PFS achieved significant, the key secondary endpoint of modified EFS was to be tested at the same alpha level. If modified EFS was significant, then CR rate and overall survival were to be tested. For overall survival, the trial was planned with 52 percent power to detect an overall survival hazard ratio of 0.73.

In the POLARIX trial, PFS is defined as time from the date of randomization until the first occurrence of disease progression or relapse as assessed by the investigator or death from any cause. Before discussing the applicant's primary PFS analysis and censoring rules, I would like to clarify that new anti-lymphoma treatment, or NALT, in the POLARIX trial included all new treatments for diffuse large B-cell lymphoma.

The protocol permitted preplanned

radiotherapy, which was not considered new anti-lymphoma treatment. New anti-lymphoma therapy could be initiated for efficacy reasons like progressive disease or toxicity and tolerability reasons. Of note, the applicant's primary PFS analysis was not censored for new anti-lymphoma therapy. For example, if a patient initiates new therapy in the absence of progressive disease, the PFS assessment continues following the new therapy; therefore, it is difficult to separate the effect of the investigational drug from the effect of subsequent new anti-lymphoma therapy.

With that background context in mind, the first topic that we will highlight is a modest PFS benefit of pola+R-CHP. This table and Kaplan-Meier curve shows the results of the applicant's primary analysis of PFS. The PFS results demonstrated a statistically significant hazard ratio of 0.73. Median PFS was not reached for either arm.

Although the difference in PFS was statistically significant, we note that the effect size with pola is modest with a 4 percent absolute

improvement of PFS at 1 year and a 6.5 percent absolute improvement at 2 years. Further, it remains challenging to assess the contribution of effect of pola specifically given the uncertainty about the activity of vincristine.

FDA considers censoring for NALT and missed assessments as important analyses to adequately assess PFS and is a typical approach for lymphoma products. This table shows the original PFS analysis in addition to some of the sensitivity analyses that the FDA conducted to better evaluate the robustness of the PFS result. The first row shows the applicant's original PFS analysis that was not censored for NALT or missed assessment. The second row shows a sensitivity analysis for PFS that censored NALT but not missed assessment. The third row shows the result based on an analysis approach that has been generally conducted in lymphoma at FDA, censoring for NALT and missed assessment.

Note that regardless of the sensitivity analysis and censoring rules, the PFS results are

modest. The upper bounds of the confidence intervals for the hazard ratio are near or greater than 1.

This table shows additional sensitivity analysis specifically regarding NALT. This was conducted because FDA identified some discrepancies in the applicant's NALT categorization. These analyses also show consistency with the primary PFS results. Although given the modest results, a sensitivity analysis that FDA frequently utilizes, IRC assessments of PFS may have been helpful; and IRC did review all responses; however, IRC assessment of PFS was not performed.

This slide shows the forest plot of PFS results by subgroup. The purpose of this subgroup analysis is to evaluate the consistency of the treatment effect across the population without any formal comparison. Limitations of subgroup analyses are acknowledged. I would like to highlight the different PFS results by lymphoma subtype indicated at the bottom of the figure. These findings suggest the heterogeneous effect.

While these analyses are hypothesis generating, the results can help inform an understanding of the treatment effect.

Now I will cover the overall survival results from the POLARIX trial. Overall survival is a clinically meaningful objective measure assessing both safety and efficacy. We acknowledge that trials with a primary endpoint of PFS may have inadequate power to detect a statistically significant improvement in OS, but FDA relies on analysis of OS, even if descriptive, to improve the benefit-risk. Overall survival plays an important role in the benefit-risk determination of a drug in the context of the totality of data.

Shown here is a Kaplan-Meier plot of the final analysis of overall survival with a median follow-up of over 3 years. As shown in the figure, pola+R-CHP did not demonstrate an improvement in overall survival over R-CHOP. The curves were similar for both arms, but at some early time point, the overall survival rates were numerically lower in the pola+R-CHP arm. The FDA evaluated the

reasons for this and did not identify any evident trends based on the available data; however, limited information was available for some deaths.

There is uncertainty associated with the overall survival results from POLARIX, which was low event rate. Nevertheless, the lack of an improvement in overall survival, particularly in the context of frontline therapy for diffuse large B-cell lymphoma is a reflection of safety and efficacy and adds to the uncertainties in benefit-risk.

Shown here is the forest plot for overall survival results by subgroup. Similar to the PFS subgroup analysis results, we again see different overall survival results based on lymphoma subtype. We will further discuss the results during the discussion on patient heterogeneity in POLARIX.

Now I'd like to transition to a discussion of the other efficacy endpoints, including CR rate, event-free survival, duration of response, and disease-free survival. This table shows the analysis of response rates in POLARIX. As shown,

pola did not demonstrate an improvement in CR rate, which was an alpha allocated endpoint. Along with no statistical significance, there is little difference in the absolute CR rate, 4 percent; however, the applicant has made efficacy claims based on numerically higher overall response rate and CR rate in the pola+R-CHP arm.

This table shows the modified event-free survival results. The definition of PFS included 4 events: disease progression; deaths; initiation of NALT due to efficacy reasons; and positive biopsy for residual disease after treatment completion. Modified EFS was an alpha allocated secondary endpoint, which was tested after PFS achieved statistical significance. The difference in modified EFS was statistically significant; however, similar to the primary PFS results, the difference is modest with a difference of 6.2 percent at 2 years.

This table shows the data for duration of response and disease-free survival. These are other secondary endpoints that the applicant

analyzed, but FDA's reliance for evaluation of efficacy is primarily based on alpha allocated endpoints. Disease-free survival was defined as the time from the date of the first occurrence of a documented CR to the date of relapse or death from any cause for the subgroup of patients with the best response of CR. Disease-free survival is equivalent to duration of complete response.

These endpoints also have several limitations. First, the results are modest. Second, given that they are based on non-randomized subsets of patients and type 1 error rate was not controlled, they are considered exploratory, and caution should be taken in interpreting the comparison between treatment arms. Third, similar to the primary PFS analysis, the applicant's analyses do not censor for new anti-lymphoma therapy, which makes it difficult to separate the effects of the investigational drug from the effect of subsequent therapy.

Next, I will discuss the heterogeneity of the study population. These figures show the PFS

and OS results by lymphoma subtype. We can see that the treatment effect appears to be heterogeneous across subtype. In patients with high-grade lymphoma, the results favor the pola arm, but as previously mentioned, the use of R-CHOP as a comparator arm raises concerns, and these patients have very aggressive disease. In the larger subgroup of diffuse large B-cell lymphoma and OS, there is a favorable PFS result with overall survival results that suggest a more favorable outcome with R-CHOP.

Shown here is the Kaplan-Meier plot of the final analysis of overall survival in the diffuse large B-cell lymphoma and OS subgroup, which included a total of 740 patients or 84 percent of the trial population. Note the overall survival has a ratio of 1.02 with an upper bound of 1.49. One year overall survival estimates were 91.8 percent with pola+R-CHP versus 95.5 percent with R-CHOP, favoring the R-CHOP arm; however, there is uncertainty in the point estimates as evidenced by the wide confidence interval.

Nevertheless, these results are concerning and should be considered in the assessment of benefit-risk.

This table summarizes the key efficacy results for the lymphoma subgroup. As mentioned, the treatment effects of pola+R-CHP appears heterogeneous across lymphoma subtypes based on PFS, OS, and CR rate. Specifically, the results tend to favor the pola+R-CHP arm, where the high-grade B-cell lymphoma subgroup has variable results for the diffuse large B-cell lymphoma NOS subpopulation and favor the control arm for the other large B-cell lymphoma subgroup. Of note, the FDA evaluated the baseline characteristics and high-level safety findings of the lymphoma subgroup and did not identify any major differences. Thus, the results suggest a heterogeneous treatment effect.

To summarize the main topics of discussion, pola+R-CHP demonstrated modest PFS benefit over R-CHOP and did not improve CR rate. Pola+R-CHP did not improve overall survival, and there is concern

about the true effect on survival based on limited information. Additionally, the results of other secondary endpoints are also modest. Finally, as discussed, the results suggest a heterogeneous treatment effect among this subpopulation.

Now I will discuss other topics, including safety, dosing, and inadequate assessment of patient-reported outcomes. These tables show a summary of selected safety findings in POLARIX. In general, the safety findings were comparable across the arm. A few adverse events occurred more often in the pola arm, including febrile neutropenia, infection, nausea, and diarrhea. The incidence of neutropenia was similar between arms, but this is likely underestimated given that labs were mandated once at the beginning of each cycle.

There was also higher incidence of febrile neutropenia in the pola+R-CHP arm despite receiving prophylactic mandatory filgrastim in over 90 percent of the patients in both arms. Additionally, there were more infections with pola; however, this did not translate into more deaths in

the pola+R-CHP arm. Lastly, the rate of peripheral neuropathy was similar across arms; however, fewer patients had recovery of peripheral neuropathy in the pola+R-CHP arm.

To support the evaluation of safety, a review of the data to support the selected dose of pola was conducted. In general, there was very limited dose exploration of pola in patients with previously untreated diffuse large B-cell lymphoma and in combination with R-CHP. Due to the limited data from doses besides 1.8 milligram per kg, it is unknown if lower doses could reduce toxicity without impacting efficacy in previously untreated diffuse large B-cell lymphoma.

ER analysis in subjects with previously untreated diffuse large B-cell lymphoma did not identify any association between exposure and CR rate, and the relationship between dose and efficacy is still unclear. However, higher rates of adverse events, including grade 3 and above febrile neutropenia and grade 3 and above infection shown in the figures, were associated with both

higher antibody conjugated MMAE and unconjugated MMAE exposure. The optimal dose in terms of safety and efficacy has not been determined.

For the last topic, I will discuss the FDA assessment of the POLARIX patient-reported outcome data. PROs are of importance for the agency, and we commend the applicant for including PRO assessment in the POLARIX trial. Based on the FDA's evaluation of the PRO data, we have the following comment.

First, the PRO assessment strategies were inadequate to measure tolerability or to support that there was not a detriment in the pola+R-CHP arm. Second, patient-reported outcomes were sparsely collected in the POLARIX trial. Although fact subscales were included in the trial, the FACT GP5 item regarding overall side effect bother was not administered to patients.

Completion rate for these PRO measures was high and symmetric up to the follow-up month 12, with completion rates greater than 80 percent for all measures throughout the time period. Third,

the applicant included patient-reported outcomes as exploratory and descriptive endpoints without multiplicity adjustment.

Fourth, FDA focuses its PRO analysis on tolerability, and from the collected PRO data, FDA notes that there was a higher proportion of patients who reported diarrhea and decreased appetite with the pola+R-CHP compared to R-CHOP during the treatment period, but otherwise, no major differences between arms.

And fifth, the applicant states in the briefing materials that no detriment global quality of life during treatment was observed with pola+R-CHP compared to R-CHOP; however, FDA disagrees with this statement. Lack of superiority is not suitable evidence for claims of comparability. The PRO assessment strategy, including the selected instrument, PRO assessment frequency, and PRO endpoints, were not adequately designed to make this claim.

In conclusion, the primary PFS analysis and various sensitivity analyses all demonstrated a

modest benefit for pola+R-CHP. The largest difference in the 2-year PFS rate was 6.5 percent. Additionally, the PFS benefit did not translate into a benefit in CR rate, and there was lack of an overall survival benefit and substantial uncertainty in the overall survival results.

Additionally, the heterogeneity of the trial population and outcome with respect to histologic subgroup impacts the interpretability and generalizability of the trial findings. Outcomes consistently favored pola+R-CHP in the minority of patients with high-grade B-cell lymphoma, where the adequacy of R-CHOP is questionable and more intensive regimens are generally preferred. In the larger subgroup of diffuse large B-cell lymphoma NOS, the PFS effect was modest. There was no appreciable difference in CR rate, and most notably, the overall survival hazard ratio exceeded 1 and raised concern.

Given the uncertainties with the PFS and OS results and challenges with assessing the contribution of effect of pola specifically, the

question arises whether, based on on the totality of data, the benefit-risk for polatuzumab vedotin in patients with large B-cell lymphoma in the frontline setting, its curative intent is favorable.

Here, I present the discussion topics. First, we would like the committee to discuss the benefit-risk profile of pola+R-CHP for the proposed patient population with large B-cell lymphoma, including patients with diffuse large B-cell lymphoma and NOS, considering the results of the POLARIX trial.

Second, based on the results of the POLARIX trial, specifically the overall survival results, please discuss whether additional follow-up data from POLARIX should be required to inform the benefit-risk of polatuzumab vedotin in patients with large B-cell lymphoma in the frontline setting.

And here, I present the voting question. Given the results of the POLARIX trial, does polatuzumab vedotin have a favorable benefit-risk

profile in patients with previously untreated large B-cell lymphoma, including diffuse large B-cell lymphoma NOS? I conclude my presentation here. Thank you.

Clarifying Questions to Presenters

DR. GARCIA: Thank you, Dr. Yazdy.

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

Finally, it would be helpful to acknowledge the end of your question with a thank you or end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

So maybe I'll just start. Thank you again,

all, for great presentations. I'd like to actually start with a question for Genentech for Dr. Fuchs and his team, and perhaps a bit ignorant from my part.

I'm not a malignant hematology person, but in your presentation, Dr. Fuchs, you clearly stated in the POLARIX scientific hypothesis what's mainly obviously replacing vincristine with polatuzumab vedotin. I understand the ADC conjugate and the potential peripheral neuropathy issues that the agent itself can lead to, but can you comment as to the true biological background behind that combination? It seems that all the data that we have had with R-CHOP, we're trying to actually compare R-CHOP with new standard regimens that have been either additive or synergistic in nature.

So I'm trying to understand if there was any biological background behind that combination up front, or if it was just -- as we traditionally tend to do in drug development in oncology -- that it works in the second-line setting, so let's just move it up front in the frontline setting,

recognizing obviously that this was a substitution trial. So I'm trying to understand the biologic background behind that, if you don't mind.

DR. FUCHS: Dr. Garcia, this is Charlie Fuchs. To your question, I think the intent of POLARIX was to look at two distinct regimens of frontline therapy, the first being historic R-CHOP, which has, of course, been the long-time standard of care, and then pola+R-CHP, which, as you rightly point out, polatuzumab is replacing vincristine. The biology of that ADC, as we mentioned, is that CD79b is expressed ubiquitously on large-cell lymphoma, and it's design to allow delivery of a microtubule agent, and we think in a more precise manner that improves benefit-risk.

But let me turn to Dr. Lee, the medical monitor of the trial, just to offer up any additional background.

Dr. Lee?

DR. LEE: Thank you. Calvin Lee with Genentech. Could we have slide 5 of the core deck, please?

This is the mechanism of action slide of polatuzumab vedotin with malignant detailed B cells. The development of polatuzumab vedotin was done probably in different detailed malignancies in a nonclinical setting, looking at whether the CD79b antigen was expressed. CD79b is a core component of the B-cell receptor, which is present on mature B cells, and specifically mature B-cell lymphomas.

So looking at B-cell malignancies broadly, we looked for expression of CD79b in pre-B cells, pro B cells, mature B cells, and of course plasma B cells, and found that the ubiquitous expression was really in the mature B-cell subset. So our development program has been primarily in these types of B-cell malignancies, where CD79b is, by nature, expressed in the malignancy.

The other component of this is that for this trial of vincristine, the payload, or MMAE, is a microtubule inhibitor which has the same mechanism of action as vincristine; therefore, the targeted and specific approach of a more potent small

molecule without systemic delivery of the agent was the real scientific basis for the study and design. Thank you.

DR. GARCIA: Thank you. If I can further expand perhaps my question, I'm sure that you in the backend of your trial development -- was there ever a consideration as to doing polatuzumab vedotin with R-CHOP, including vincristine, or was this simply not done because of the concerns of perhaps exacerbated increase in the incidence of peripheral neuropathy?

DR. FUCHS: Of course, Dr. Garcia. Let me return to Dr. Lee.

DR. LEE: Thank you. Calvin Lee with Genentech. Certainly this is something that we as a program considered; however, we saw other programs, other antibody drug conjugates, using an antibody drug conjugate with the payload of MMAE, which combined vedotin antibody drug conjugate, specifically brentuximab vedotin, with R-CHOP, with diffuse large B-cell lymphoma patients, and this combination resulted in an unacceptable high rate

of neurotoxicity, which is what we thought would happen as well if we were to do the same combination. And for this reason, we avoided that addition in the study. Thank you.

DR. GARCIA: Thank you.

Let's move on to other committee members.

Dr. Nowakowski, do you have a question or a comment?

DR. NOWAKOWSKI: Hi. Thank you, Dr. Garcia. Greg Nowakowski. I have a couple of clarifying questions to the efficacy to the sponsor, and also one question regarding a pathology review. So maybe I'll start from a [indiscernible] standing.

If you could pull up sponsor's slide 27, which shows the PFS analysis, I think those curves illustrate wide -- in the lymphoma community we have difficulty interpreting results of the POLARIX trial in addition to some of the issues mentioned by FDA colleagues.

If you look at these PFS curves, they separate practically [indiscernible] late in aggressive lymphoma. We typically would expect

those two to separate earlier, which means that treatment had relatively little impact on reducing the number of patients with primary refractory disease or relapsing early, which is actually reflected also in a similar overall response rate and CR rate.

Now, what it also means is that the treatment effect appears to be on relapses, which happen later on, which typically are associated with the better outcome than patients with primary refractory disease, and maybe that's one of the reasons, or possible reasons, why this difference in overall survival is more difficult to show in this study. But it will also occasionally be driven by an unusual type of relapse, which is delayed in time, and such relapse would be a potential for CNS relapse. Those events tend to occur a little bit later.

So I was curious if the sponsor has any data in regards to incidence of CNS relapse, isolated CNS relapse in those arms. And I know that there was prespecified prophylaxis used, methotrexate

allowed in the study, so I would be curious about the overall rates of use of prophylaxis in this study.

DR. FUCHS: Dr. Nowakowski, there are several components to your question, and I want to make sure we answer all of it. I'm going to turn to Dr. Lee to answer your question about the nature of relapses and prophylaxis, and then ask Dr. Friedberg to respond regarding the interpretation of the PFS benefit seen in the study. So let me start with Dr. Lee.

DR. LEE: Thank you. Calvin Lee with Genentech. With respect to CNS prophylaxis administered in the trial, this was something either intrathecal methotrexate, and in some cases, after the fact, systemic high-dose methotrexate. The incidence of CNS prophylaxis was approximately 20 percent in each arm. Additionally, the incidence of isolated or systemic with CNS relapse included was similar between the two treatment arms, a total of 2.7 percent and 2.9 percent with CNS relapse detected. Thank you.

DR. FUCHS: Dr. Friedberg?

DR. FRIEDBERG: This is Jonathan Friedberg. Thank you, Dr. Nowakowski, for that insight. I'll first agree with you that this treatment did not appear to have a substantial impact on true primary refractory disease, but as you can see from these curves, as well as other studies, that's an uncommon event in the R-CHOP era.

These curves start to separate, and the separation grows over time, prior to the 1-year time point. And in fact, as was shown in the presentation, there's already a significant difference at 1 year between these two curves. Most of the events that occur in diffuse large B-cell lymphoma occur between month 6 and month 24, so the majority of the events that could be impacted by the treatment are covered certainly by the treatment and, again, the durability is shown at least through month 36 and beyond in this curve.

I think the issue about CNS is an interesting question. There's some series of studies that suggested CNS relapse, if it occurs,

it may occur very early. Others, there are reports of late CNS disease. In the study and certainly what's been reported, there do not appear to be significant differences.

DR. NOWAKOWSKI: Thank you, Dr. Fuchs and Friedberg. If I can just pull up a couple more clarifications regarding the efficacy analysis in relation to overall survival, the study was allowing patients with IPI 2 to 5. Patients of IPI, too, have significantly better outcomes than 3 to 5, and I was wondering if you could show us the progression-free survival curves and overall survival curves, if you have, for patients with IPI 3 and above.

DR. FUCHS: Dr. Nowakowski, I don't think we have those Kaplan-Meier curves available, but let me turn to Dr. Lee just to describe what we have in terms of the IPI subsets.

DR. LEE: Thank you. Perhaps we can bring up the efficacy slide 6 on the screen. This is Calvin Lee with Genentech. With respect to the different subgroups by clinical factors, by IPI,

the point estimate for the forest plot hazard ratio for progression-free survival of IPI was close to 1, and IPI 3 to 5 was just under 0.7.

As Dr. Nowakowski mentioned, the outcome for these patients is different with the estimated 2-year progression-free survival of IPI 3-to-5 patients in the 50 something percent range compared to the high 70s for the patients treated with R-CHOP. With respect to the pola+R-CHP arm, the outcome for the IPI 3-to-5 patients was also higher with a similar IPI to your PFS in the pola+R-CHP arm.

I think the other aspect of both these clinical factors is, within this forest plot, it's important to look at IPI as a component score, and when looking at the individual components of clinical risk, the point estimates of the patients with higher and lower risk factors tend to favor the pola+R-CHP arm. Thank you.

DR. FUCHS: Let me, just as well, just turn to Dr. Flowers because I know he had discussed IPI in his presentation.

Dr. Flowers?

DR. FLOWERS: Thank you, Dr. Fuchs. Chris Flowers from MD Anderson.

One thing that's important to consider when we look at unplanned subgroup analyses, that they are just that. They can be used as exploratory analyses for the design of future trials. As I discussed in the preliminary remarks, that when you look at all patients treated in prior first-line clinical trials with R-CHOP, again, the largest analysis that had ever been done looking at IPI in that setting with more than 5800 patients, that those patients with IPI 2 through 5 within each of those groups had worse outcomes and are the patients that truly had an unmet need. So I see those as the patient population who are eligible for this trial with the overall benefit, that have a benefit in the PFS advantage that's seen in the trial.

DR. NOWAKOWSKI: Thank you, Drs. Flowers and Fuchs. That's helpful. I guess what I wanted to clarify is what impact on overall survival you see

on those high-risk patients 3 to 5, if you have any additional data there.

DR. FUCHS: Dr. Nowakowski, just to clarify, you're asking for overall survival by those subgroups?

DR. NOWAKOWSKI: Correct. You show a PFS. I was hoping to see the curve, but that's ok. But do you have a forest plot like this for overall survival as well for those high-risk groups?

DR. FUCHS: Of course. Let me turn to Dr. Lee again to answer your question.

DR. LEE: Thank you, Dr. Nowakowski. With respect to the overall survival by these two different subgroups, the point estimate hazard ratio, or IPI 2, would be 0.94, while the point estimate for the IPI 3 to 5 is 0.91, both favoring the pola+R-CHP in the exploratory analysis of these subgroups in overall survival. Thank you.

DR. NOWAKOWSKI: Thank you. This is very helpful. I thank you for those clarifications.

My last question, switching gears a little bit to the central pathology review, I did notice

that the study protocol and paper mentioned the central pathology review. For lymphoma, we frequently have a large discrepancy between the central pathology review and local pathology review due to interpretation, particularly between some of the low-grade lymphoma patients with grade 2 for local lymphoma and large-cell lymphoma, and also the subset of the patients mentioned by our FDA colleagues, the high-grade lymphoma.

I was wondering if you could share results of the central pathology review and how this was compared and applied to the study.

DR. FUCHS: Of course. Let me turn to Dr. Lee with regard to the specifics within the trial. As well, I'll ask Dr. Flowers just to comment on the process in general.

Dr. Lee?

DR. LEE: Thank you. Calvin Lee with Genentech. Central pathology review was performed for diagnosing different specific subtypes of aggressive lymphoma that's been of interest in many clinical trials and development of new therapeutic

options and the subtyping. Specific central diagnostic testing was performed for cell of origin using the NanoString assay, the amino histochemistry of MYC and BCL2, and then FISH, which is fluorescence in situ hybridization, detecting rearrangements of MYC and BLC2, and in the case that there was also a MYC rearrangement already, BCL6.

These were really the main tests that were performed. The local cytopathologic diagnosis that was reported earlier, the concordance of this, as you're aware in some of the other studies, is something that does not necessarily have as much overlap with the subtyping, although the overall diagnosis of large B-cell lymphoma can comfortably be confirmed based on the central testing compared to the local testing. One example of this is, the concordance of the patients who were essentially confirmed to have double- or triple-hit lymphoma was identified in approximately 20 percent of the local testing.

But that's just one flavor of that. I'll

pass this on to also Dr. Flowers for further comment. Thank you.

DR. FLOWERS: Thank you, Dr. Lee.

Chris Flowers from MD Anderson. As I mentioned at the outset of my talk, there is broad agreement within community-based practices and academic practices on the diagnosis of large B-cell lymphoma, and that global diagnosis can be made readily in community-based practices. But there are differences, as you alluded to in your comments, Dr. Nowakowski, between the local or site-specific subtyping.

I'll maybe just point out one of those areas around the site-specific subtyping data that you saw with the local data that were presented by the FDA, these subgroups are quite complex, and even experts don't agree across these diagnoses, and in fact the experts have changed their classification of these.

One of the subgroups that were listed there as double-hit lymphoma within the presentation, the combination of BCL6 and MYC translocation is no

longer considered in the 2022 classification as a double-hit lymphoma, and it's been reclassified as diffuse large B-cell lymphoma not otherwise specified or high-grade B-cell lymphoma not otherwise specified.

I have a slide to potentially show you how complex this is. I'm not going to show it just in interest of how ridiculously complex this new classification system is unless others would like to see it. I think really an important point here is that when you're looking at these subgroups, that unplanned analyses are exploratory and hypothesis generating for future trials, and in this setting, with a cd79b conjugated antibody, or conjugate, that the mechanism of action is expected to work across all mature B cells, so it should be applicable to all mature B-cell lymphoma subtypes.

DR. NOWAKOWSKI: Thank you, Dr. Flowers and to the sponsor for those certifications. So if I understand correctly, this central review was not done to confirm the diagnosis but mostly to look for this additional subtypes with more

classification primarily. That's correct?

DR. FUCHS: Dr. Nowakowski, that is correct.

DR. NOWAKOWSKI: Okay. Well, thank you. That's the end of my questions. Thank you.

DR. GARCIA: Thank you all.

Maybe before we continue with committee questions, I know Dr. Kasamon from the FDA has some comments to make.

Dr. Kasamon?

DR. KASAMON: Thank you, Dr. Garcia. This is Yvette Kasamon. FDA would like to make some additional comments about the overall survival outcomes according to IPI risk stratification. I'd like to turn it over to Dr. Yazdy, and we would like to project the core slides from FDA, please. Thank you.

DR. YAZDY: Thank you.

This is Maryam Yazdy. I'm going to project our overall survival analysis and subgroups to point out a few things that was a question from the sponsor and applicant and discussed. I would like to point out this is the overall survival subgroup

analysis, the final analysis. Please note the IPI 2 and IPI 3 to 5, I would like to point out that in the IPI two subgroup of patients, the overall survival hazard ratio was over 1. It is 1.08, the upper bound of 2.18. For the patients in the IPI of 3 to 5, the hazard ratio for overall survival is 0.9. Thank you.

DR. GARCIA: Thank you.

Continuing with committee members, Dr. Sekeres, thank you for your patience.

DR. SEKERES: Thank you so much, Dr. Garcia. I wanted to Circle back to the Pathology question. I don't think I actually heard an answer to Dr. Nowakowski's question about central versus local review of pathology in the agreement there. I understand that there are new classification systems that have come out that have made this even more complicated -- believe me, we are wrestling with this in myeloid malignancies as well -- but what was the agreement between local review and central review in a diagnosis of diffuse large B-cell lymphoma versus high-grade lymphoma?

DR. FUCHS: Dr. Sekeres, let me, again, return to Dr. Lee to address your question.

Dr. Lee?

DR. LEE: Thank you, Dr. Sekeres. This is Calvin Lee. Local diagnosis was based on the local pathologist, and the instruction was based on the WHO 2015 guidelines for diagnosis of diffuse large B-cell lymphoma and the various mature B-cell subtypes. From central testing, testing was performed with FISH to detect MYC rearrangements, BCL2 and BCL6 rearrangements that would detect double- and triple-hit lymphoma.

DR. FUCHS: Let me just also turn to Dr. Flowers with regard to how we conducted the analysis.

DR. SEKERES: Actually, could you not go to Dr. Flowers. I want to go back to Dr. Lee. That still really wasn't an answer. What was the agreement between local and central for diffuse large B-cell lymphoma and for high-grade lymphomas?

DR. LEE: Thank you. We did not perform central pathologic testing for the diagnosis.

DR. FUCHS: If I may just turn to Dr. Flowers, please.

Dr. Flowers?

DR. FLOWERS: Thank you, Dr. Fuchs. Chris Flowers here. The intent from the steering committee for this trial was that this trial be one that could be readily accessible by community providers who currently provide R-CHOP therapy to patients based on a community diagnosis of diffuse large B-cell lymphoma, or now large B-cell lymphoma, so that community diagnosis was used as a component for making treatment decisions. The central pathology review in this study was really used predominantly for exploratory analyses to be able to look at these subsets, not for confirming the diagnosis.

We've also seen in prior clinical trials using diffuse large B-cell lymphoma that central pathology review slowed down the conduct of the trial to a degree that it impacted the ability to enroll patients, including our randomized-controlled trials that were conducted by some of

the august panel members that are present.

DR. SEKERES: Yes, I totally get that. This is considered a medical urgency, if not emergency, to treat these patients who don't want to wait for central review, but let me just try to summarize what I just heard. So central review to confirm the diagnosis was not performed.

DR. FLOWERS: Correct.

DR. SEKERES: Thank you.

Next question for you, and this is for Dr. Flowers.

Chris, God forbid I have a large-cell lymphoma, I would cross state lines into the great state of Texas to see you as my doctor. You're a great doctor, and during the summer months after Rochester's thawed, I'd go and see Dr. Friedberg as well. That's actually a true statement, in addition to the doctors in my own division who are fabulous.

If I came to you with a high-grade B-cell lymphoma, would you treat me with this regimen?

DR. FUCHS: Dr. Flowers?

DR. FLOWERS: Thank you, Dr. Fuchs.

When we look at the general diagnosis of high-grade B-cell lymphoma not otherwise specified, the current standard of care for those patients has been R-CHOP historically. There is a specific subtype based on phase 2 data, the double-hit lymphomas, where we might consider other more aggressive data, but there are no randomized phase 3 data to suggest that there is a regimen that is better than R-CHOP.

DR. SEKERES: It's interesting. Most presentations to ODAC, you see somebody throw up some slides from the NCCN, but you all didn't do that. When I went to the NCCN and I plugged in there high-grade lymphoma, it takes me right to regimens like CODOX or much more intensive regimens as the preferred frontline therapy. You're saying that your preferred frontline therapy, if I had a MYC abnormality, would be R-CHOP and not something more aggressive?

DR. FLOWERS: The particular group that we're talking about here is the group that you

would call the double-hit diffuse large B-cell lymphoma, which is a subset of the high-grade B-cell lymphoma. There was a period of time where high-grade B-cell lymphomas were also considered to be a group that we would treat with more aggressive regimens, but that group is a group where R-CHOP would have been a standard approach.

Maybe I'll have Dr. Friedberg also comment here.

DR. FUCHS: Even though it remains cold in Rochester, why don't we let Dr. Friedberg also answer that question.

DR. FRIEDBERG: Thank you, Dr. Fuchs. Jonathan Friedberg.

I think what's happened over the last years is that the incidence of the diagnosis of high-grade B-cell lymphoma is going down, particularly in academic pathology laboratories. That's a morphologic diagnosis. You look under the microscope, and you say this is high-grade. What has been identified is an entity called double-hit lymphoma or the high-grade with BCL2 and MYC

rearrangements, clearly that is a unique entity, and I think many academic institutions would consider a more aggressive regimen for that subset of patients.

However, in this study, based on local review, the number of patients with high-grade B-cell lymphoma that actually then on central review had a MYC and BCL2 abnormality, it did not match up. There were many patients with high-grade B-cell lymphoma morphology that did not have the genetic changes. Most of those patients in academic laboratories would likely be signed out as diffuse large B-cell lymphoma because, again, the push is now to use the high-grade histology to really identify the molecular lesion rather than a morphologic lesion.

To specifically answer the question that was raised by Dr. Sekeres, if I saw a patient with high-grade B-cell morphology, find out in the community or even agreed to in my institution, that was not double hit, I would use an R-CHOP-based regimen, and I would certainly consider using this

regimen if it were approved. If the disease was double hit, I think that's where we're looking for clinical trials, and we sometimes consider more aggressive regimens.

DR. SEKERES: Thank you, Dr. Friedberg.

Then let me just push you guys a little bit more. So let's say I came to Rochester or to Houston, and I had a GCB lymphoma. Would you treat me with this regimen or would you treat me with something different?

DR. FUCHS: Dr. Friedberg and Dr. Flowers, you want to answer, please?

DR. FLOWERS: Thanks. Chris Flowers. Go ahead, Jonathan.

DR. GARCIA: This is Jorge Garcia. I understand the nature of the question. I think it's a very thoughtful one from Dr. Sekeres. I think since the question is simple, would you or not use me [indiscernible], and I predict that clinically we all will have to see the patient in person, ask for the history, the background, physical findings, and whathaveyou, but if we can

shorten our answers to Dr. Sekeres' question, that would be great.

DR. FUCHS: Of course.

Dr. Friedberg, do you want to start?

DR. FRIEDBERG: To be short, absolutely I would treat a patient with GCB lymphoma with polatuzumab vedotin R-CHP.

DR. FLOWERS: And my answer is the same. Absolutely, I would treat a patient with GCB. I would treat all patients who are eligible with R-CHP in that manner [indiscernible].

DR. SEKERES: Okay. Thank you.

DR. GARCIA: Thank you.

Dr. Dunleavy, do you have a question?

DR. DUNLEAVY: Yes. Hi. This is Kieron Dunleavy. It's only two questions.

The first question is about the heterogeneous treatment effect that was seen in the 93 patients with high-grade B-cell lymphoma compared to DLBCL NOS. Other studies in aggressive B-cell lymphomas have shown that this subset has more adverse IPI characteristics. What was the

difference in IPI characteristics and those clinical characteristics in the high-grade B-cell group compared to the DLBCL NOS group?

DR. FUCHS: Of course. Let me turn to Dr. Lee, and then Dr. Flowers as well, if you have anything to add.

Dr. Lee?

DR. LEE: Thank you. Calvin Lee with Genentech. When we looked at the -- maybe I'll speak to the centrally confirmed double- and triple-hit patients that were identified in the study. The incidence of IPI, for example, the distribution, was similar to that observed in the IP population with approximately 35 percent IPI 2 and 65 percent IPI 3 to 5.

Does that provide some context to what you're asking, Dr. Dunleavy?

DR. DUNLEAVY: Yes. That's fine, actually. Thank you. Thank you for clarifying that.

The other question that I had was in the high-grade B-cell lymphoma subgroups, what was the time from initial diagnosis to start of treatments,

and how did that differ compared to the DLBCL NOS group?

DR. FUCHS: Dr. Lee?

DR. LEE: Thank you. Among the same double- and triple-hit centrally confirmed patients, the median time from diagnosis was actually not different from that of the ITT population, between 26 and 28 days from diagnosis, meaning the time of the biopsy and initiation of the treatment. Thank you.

DR. DUNLEAVY: And the third question was, in terms of the pathology, and we discussed central pathology review, were there any criteria for obtaining the FISH analyses? Considering that there was probably a huge heterogeneity, were there any specific guidelines in the protocol for FISH testing, or could any lab be used, or what did the protocol specify?

DR. FUCHS: Of course.

Dr. Lee?

DR. LEE: Thank you. Calvin Lee with Genentech. For local testing, FISH was not

mandated at the site; so 2016-2017 updated for lymphoma class patients. Even though FISH testing was recommended, it was not required; however, we required tissue collection for all patients enrolled and performed central FISH testing for all patients, and that is the basis for our results for the double- and triple-hit patients. Thank you.

DR. DUNLEAVY: Thank you.

DR. GARCIA: Dr. Pai?

(No response.)

DR. GARCIA: Dr. Pai, do you have a question? Maybe you're muted.

(No response.)

DR. GARCIA: Okay. Let's just move on in the interest of time with Dr. Sung.

Anthony?

DR. SUNG: Anthony Sung. As FDA pointed out, applicant's PFS analysis was not censored for new anti-lymphoma treatment, and I was wondering if the applicant could expand upon why, as well as that there were differences in new anti-lymphoma treatments between the two groups in the absence of

relapse.

DR. FUCHS: Of course. Let me turn to Dr. Lee just to specifically address the logistics of that work, and then Dr. Friedberg if he has any additional comments.

Dr. Lee?

DR. LEE: Thank you. This is Calvin Lee with Genentech. If I could have core slide 28 up, please?

This is a slide that Dr. Hirata walked through, indicating the three different methods for PFS analyses that includes different types of censoring for subsequent therapies. As mentioned, the primary analysis did not incorporate any censoring for subsequent treatment given that our main question in the study was to see whether or not the initial treatment had an impact on the time of disease progression, death, or relapse, at any time point.

The main difference that we actually observed is that in censoring for subsequent treatment, prior to disease relapse or in the

absence of disease relapse, there were more patients who would be censored in the R-CHOP arm than in the pola+R-CHP arm for various reasons, including, for example, something that was detected in that event-free survival analysis. Residual disease at the end of therapy was detected in 6 patients in the R-CHOP arm and zero patients in the pola+R-CHP arm; and oftentimes, residual disease does not actually represent disease progression because they can be part of a partial response, which may drive subsequent treatment, for example.

The other primary scenario, in addition to some of these CNS prophylaxes with high-dose methotrexate, which was sometimes administered after the fact, would be when toxicity led to additional therapies. In this particular treatment regimen, between the two treatment arms there were 16 patients in the R-CHOP arm who discontinued due to toxicity and received subsequent therapy in the absence of disease progression, and some ultimately did have disease progression; and there were eight

who had toxicity who stopped study treatment in the pola+R-CHP arm.

With these two examples, they give some clinical scenarios, which led to what we consider to be and what appear to be informative censoring based on subsequent treatment. Thank you.

DR. FUCHS: Dr. Friedberg, did you want to add?

DR. FRIEDBERG: Jonathan, I have nothing to add.

DR. FUCHS: Okay. Thank you.

DR. GARCIA: Thank you.

Dr. Pai, getting back to you. You had a question?

DR. PAI: Yes. Can you hear me ok now?

DR. GARCIA: Yes. Please go ahead.

DR. PAI: Okay. Sorry about that.

Dr. Yazdy's slide 41 presented an exposure toxicity relationship, so I have a question related to the dosing strategy for this compound at 1.8 milligram per kilogram. Because it's being weight-based and this is a mAb, which typically has

a small volume of distribution, were there differences in toxicity by body size and also affect? For example, underweight individuals having a lower response because they're getting a lower dosage; likewise, an obese individual getting potentially a higher dose and having toxicity?

Those are narrow --

(Crosstalk.)

DR. FUCHS: Of course, Dr. Pai. Let me turn to Dr. Lee.

DR. LEE: Thank you, Dr. Pai. This is Calvin Lee.

Perhaps we can have clinical pharmacology slide 32 up. This is the one where at least we did the analysis on patients with a higher body weight using 100 kilogram as the cutoff. And looking at the incidence of adverse events, fatal serious adverse events and high-grade adverse events, there's, in general, a similar incidence, even though of course the numbers are small. We did not form something which looked at very underweight, given that the range of body weight was primarily

that of adult patients.

Does that help provide context to the instance of toxicity associated with weight?

DR. PAI: Yes. Thank you.

I don't have any additional questions. Thank you.

DR. GARCIA: Thank you.

Dr. Vasan?

DR. VASAN: Hi. I had a question for the sponsor regarding the nature of relapses, given that patients had multiple surveillance imaging after receiving therapy, and knowing that in the setting of triple lymphoma, not all patients are getting regular surveillance imaging.

Do you have any insight into the nature of these relapses? Were patients actually symptomatic in these relapses or did they just show up on imaging, and do we have any pathologic review that can establish concordance? Thank you.

DR. FUCHS: Dr. Lee, did you want to address the nature of relapses?

DR. LEE: Thank you, Dr. Vasan. Calvin Lee

with Genentech. The protocol does schedule surveillance imaging every 6 months after the completion of therapy for the first 2 years, which would present primary time points where patients will have disease relapse in diffuse large B-cell lymphoma. There were many patients who actually had unscheduled imaging, which represent times where symptomatic or clinical suspicion may have driven the surveillance imaging.

Whether these numbers were actually relatively -- I don't have the specific numbers off the top of my head right now. We can get back to you with that information, as well, but I'm not sure if that helps provide context for the pattern of relapse observed in this study.

DR. VASAN: I guess the second question is, was there central pathological confirmation of that relapse or was that also investigator confirmed?

DR. FUCHS: Dr. Lee?

DR. LEE: Thank you. At relapse, biopsy was not mandated on the study and tissue collection was also not required, so we did not have central

testing of relapse. Thank you.

DR. VASAN: Thank you.

DR. GARCIA: Thank you.

I know Dr. Gormley from the FDA has a comment or a question.

Dr. Gormley, please go ahead.

DR. GORMLEY: Thank you, Dr. Garcia.

I just wanted to mention a couple of comments about the censoring approaches for new anti-lymphoma therapy. Generally in lymphoma, we have censored for missing assessments, and then also censored for initiation of new anti-lymphoma therapy. In that, this allows for isolation specifically of the investigational treatment in and of itself. There are considerations with either method, and generally what we're looking for is consistency of results across methods; that the results are consistent results and robust results, is sort of what we're looking for.

I'll ask my statistical colleagues to comment just a little bit further. We'd also like to pull up the FDA main slide deck in the interim

to show a slide, please.

DR. GU: Hi. My name Wenjuan Gu. I'm the statistical reviewer for this submission. Here we're clarifying that this table shows the number of events after censoring for NALT on missed assessments in each treatment arm. In the pola arm, there were seven, which accounts for 1.6 percent events that occurred after NALT and 4 events that occurred more than two consecutive missed assessments. In the R-CHOP arm, there were 16 events that occurred after NALT and 1 event occurred after two or more consecutive missed assessments.

We'd like to point out censoring 23 events, which account for 2.6 percent that caused change of statistical significance, and as we stated, regardless of the approach used, the results in PFS is modest. Thank you.

DR. GARCIA: Thank you.

Dr. Gormley, do you have any additional comments or questions from your team?

DR. GORMLEY: That's all. Thank you.

DR. GARCIA: Great.

Dr. Madan, your question?

(No response.)

DR. GARCIA: Dr. Madan, you may be muted.

(No response.)

DR. GARCIA: Let's move on with Dr. Diehl.

Dr. Diehl, do you have a question?

DR. DIEHL: Yes, I have two questions, and they're both directed to the sponsor.

The first question is, were any biopsies done at the time of relapse, and if so/if not, were SUVs collected on the PET scans? And I ask this question because of the shape of the curve, which continues to go down for both treatment arms.

DR. FUCHS: Of course. Let me ask Dr. Lee to comment on how we characterized relapse in the study.

DR. LEE: Thank you. This is Calvin Lee with Genentech. With respect to your first question, for biopsies collected, we did not require collection or central submission of biopsies at relapse, given that the ability to

procure this may be variable in the study. We did have optional collection, but the collection for this relapse tissue was low.

With respect to PET imaging, relapse, of course, may have been detected with CT based imaging as well as PET Imaging. We encourage PET imaging at relapse; however, we collected [indiscernible] for specifically rather than SUV measurement, given the variability with SUV detection across different machines globally. Thank you.

DR. FUCHS: And also, let me let Dr. Flowers, as a member of the steering committee, just comment on the approach to characterizing relapse.

Dr. Flowers?

DR. FLOWERS: Chris Flowers from MD Anderson. I think the other thing that we see within the context of this trial is that the impact of relapse, in terms of the use of subsequent therapies -- and you saw from Dr. Hirata's core deck, that she presented, the number of subsequent

therapies with stem cell transplantation, and the use of CAR-T cell in patients at relapse were numerically higher in the group that received R-CHOP compared to the group that received just the pola+R-CHP, showing that those relapses had consequences in terms of the need for subsequent therapy in the R-CHOP arm.

DR. DIEHL: Yes. Thanks, Dr. Flowers, because that goes to my second question.

With the difference in therapy, radiotherapy, systemic therapy, stem cell therapy, and CAR-T in the group that progressed, the R-CHOP group, why is that not reflected in the quality-of-life assessment? What am I missing?

DR. FUCHS: Well, let me just turn to -- of course. I'm going to ask Dr. Lee to just comment on the data, and then let Dr. Flowers more specifically answer the nature of your question.

Dr. Lee?

DR. LEE: Thank you. Calvin Lee with Genentech.

I think your question is asking why our

quality of life doesn't detect the differences observed with disease progression, and the primary reason for that is because quality-of-life measures were not collected at or after disease progression because routine clinical visits on study sees other than survival follow-up and collection for subsequent treatment. Thank you.

DR. FUCHS: Dr. Flowers?

DR. FLOWERS: Perhaps if you can bring up the core deck, slide number 33, which speaks to the point that I was making, that the differences in systemic therapy in the group show an impact in those relapses in terms of the numbers of stem cell transplants and CAR-T cell therapies that were delivered.

As someone who's done stem cell transplants for patients with lymphoma for more than 20 years now and leads one of the center's that delivers more CAR-T cell therapy than probably most centers in the world, those are therapies that can be effective therapies in the relapse setting, but as a provider who treats patients with lymphoma, it's

something that I would like my patients not to have to go through if we can avoid it.

DR. DIEHL: So I guess the hard data on benefit would come down to -- and if I add the stem cell and the CAR-T together, I get about 5 percent -- you're going to save about 5 percent of the people going through that therapy.

Would that be a fair statement?

DR. FUCHS: Dr. Flower?

DR. FLOWERS: If you go back to the patient population that I described, the hypothetical patient population from the patient journey that I described -- and perhaps if we show the patient journey slide, and I think that's slide 14 from my deck.

Thinking about now the clinical group that I lead at MD Anderson, which is a single institution group where we see approximately 500 patients with diffuse large B-cell lymphoma each year, about 25 to 35 of those patients would benefit and not need to go through those subsequent therapies.

DR. FUCHS: Dr. Friedberg, did you want to

add anything?

DR. FRIEDBERG: I'd quantify that, and the difference would be about 5 percent, right?

DR. FUCHS: Dr. Friedberg, go ahead.

DR. FRIEDBERG: Yes. This is Jonathan Friedberg. I would say I think it's very hard to quantify that because it's a very moving target on eligibility for CAR-T and autotransplant in the relapse setting.

We had six criteria for the patients who qualified for autologous transplant and those who did not, based on age, comorbidity, and other issues; and in the past, I would say that about half of patients who progressed were candidates for autotransplant.

With new CAR-T constructs coming out, the eligibility is broadening, and in fact as we've gotten more accustomed to giving CAR-T cell therapy, the older patients may be eligible for CAR-T cell treatment; however, they have more toxicity when they get CAR-T cell treatment.

So to put an absolute number, it requires a

knowledge of who's eligible for those treatments and who isn't. I think that, based on the trial experience, your number may be correct; however, I would say that it depends on the location and access to these treatments as far as what that absolute number might be, and probably that 5 percent figure is a bit conservative.

DR. DIEHL: Can we go back to slide 33? I'm trying very hard to quantify the benefit here and get it in terms. When I add up stem cell transplant differences and CAR-T differences, I get just under 5 percent. So to me, that would be that in this study, by these data, you actually had 5 percent or 5 out of every 100 people that didn't have to go through a stem cell transplant or CAR-T, which were all going to raise toxic.

Is that a fair statement?

DR. FRIEDBERG: Yes. This is Jonathan Friedberg again. I mean, I think the other way to look at these data is that you've cut the number of stem cell transplants and CAR-T in half, which is a big accomplishment for an upfront treatment to have

that impact on diffuse large B-cell lymphoma. There were 47 patients who got either stem cell transplant or CAR-T after R-CHOP and only 26 who got it after pola+R-CHP.

I think that decreasing the absolute percent is a little bit hard because, as I said, that's a moving target, and it depends on your patient population. But if you can cut the number of treatments in half, that's a meaningful benefit for patients.

DR. DIEHL: We're not going to come to agreement on this. I'm looking very hard for a benefit of progression-free survival. It didn't show up in your quality-of-life assessments because of the way they were done, and I think you have a really definite benefit here, and that's why I'm going to 5 out of 100. I know it may change in the future, but I think this is the benefit of the trial.

DR. FUCHS: Dr. Flowers, did you want to add anything?

DR. FLOWERS: I think there are two other

components here. As you know well, access to stem cell transplantation and CAR-T cell therapy are limited, and access to those potentially curative therapies in the relapse setting is another challenge that patients face, particularly when they're only available at selected centers. And to be able to avoid the need for a therapy for potentially curative therapies in the second or later lines that are difficult to access, I think it's another important benefit.

The other thing is that if you look here at this graph as well, there are the differences and total differences in systemic therapies. So not all patients are eligible, and there are other non-curative regimens that patients would need to go through if they are not able to achieve sustained progression-free survival in the first lines.

That is an additional benefit even when therapies are not curative. As you know, there would be multiple lines of therapy given to patients with the subsequent toxicity for patients,

and as a patient, all of our goals and hopes for our patients is for them to be cured in the first line. And as Jonathan said in his comments, I can't think of any time that we've had a potentially curative therapy to offer to patients what we would think about withholding.

DR. DIEHL: No, I agree with you completely. I'm just trying to put a number on it, so thank you.

DR. KASAMON: Dr. Garcia?

DR. GARCIA: Thank you.

Yes, Dr. Kasamon, I understand you have a comment or a question. Go ahead.

DR. KASAMON: Thank you. This is Yvette Kasamon. FDA would like to comment further on making statements about efficacy, based on comparing rates of new anti-lymphoma therapy. I'd like to turn it over to Dr. Yazdy. Thank you.

DR. YAZDY: Thank you, Dr. Kasamon.

Yes. This is Maryam Yazdy. I would like to briefly add FDA's position regarding new anti-lymphoma therapy, given this detailed

discussion about new anti-lymphoma therapy between the arms.

FDA disagrees with the contention that less new anti-lymphoma therapy in the pola arm necessarily indicates better efficacy. The findings of less NALT in the pola+R-CHP arm should not be used as evidence of superiority compared to R-CHOP because NALT, as we know, can be given for different reasons -- it could be toxicity or efficacy -- and has a component of subjectivity. The number of NALTs was not an endpoint due to some of these reasons, and we're cautious in the assessment of NALTs given these considerations, and we mainly rely on less biased predefined endpoints. Thank you.

DR. GARCIA: Thank you.

Dr. Madan, do you have a question?

DR. MADAN: Yes. Ravi Madan, NCI. I have a question, starting with Dr. Yazdy and her slide number 22, and it goes back, again, to this NALT concept here.

It's interesting to me that we're talking

about censoring data throwing off the statistics even though the censoring favored the R-CHOP arm in terms of the NALT therapies. So I just wondered globally, before I get to a second question, the fragility of these statistics; is it really because we're starting off with such a high bar, and is it realistic to think that without doing a multi-thousand patient trial, that you're going to get anything more than could be described as modest? That's question one.

Question two, it's really this PFS endpoint and the meaning of it. The sponsor presented a story that, basically, the 2-year PFS is an important benchmark in leading a happy life and a healthy life thereafter, and they put that in the context of the data, which shows PFS actually growing at 1 year to 2 years, and then to 3 years.

So if the FDA could comment on those two aspects. Thank you.

DR. GORMLEY: Hi. This is Nicole Gormley. Thank you for your comment and question.

I think just from the first comment, really,

about the different censoring results and the interpretation of that, and the overall benefit-risk framework, then, when we think about this, generally, when we have therapies that are really effective, this isn't a question. We see consistent results regardless of the sensitivity analyses that are performed. The main intention of prespecifying these sensitivity analyses and having various sensitivity analyses is to look for consistency of the results and the robustness of the findings. So I think when we see that there are some that are statistically significant and some that aren't, that raises some questions for us.

Additionally, I would just add that when we have effective therapy, this issue just does not come up. I can't necessarily say anything more other than I think what we see here is a modest result, and that we're also seeing some in the sensitivity analyses, some that then are not statistical significance.

With regard to your other comment, we

generally rely on the endpoints specified in the trial that have alpha allocation to draw our conclusions regarding efficacy. For safety, we look at a broad number of endpoints, a broad number of assessments, to understand the safety profile, but for efficacy, we generally tend to rely on those that are prespecified and have alpha allocation.

We look at progression-free survival, we'll look at response rate, and we'll look at CR. If OS is an efficacy endpoint without the allocation in the trial, we will evaluate that. We do not generally look at differences in NALTs that may be observed, or differences in some of these other endpoints, or PFS at 2 years, or other endpoints that are hypothesized that may be clinically meaningful. We really, for efficacy, limit our analyses to those that are prespecified with alpha allocation in the protocol.

DR. MADAN: Thank you, Dr. Gormley.

Just to clarify back to your first response there, as you said, we normally look at trials, and

the statistical robustness is self-evident. But again, my question -- and this is out of ignorance on my part -- is how much of the statistical fragility here is due to the fact that we're starting at 70 percent and improving upon that, as opposed to starting at a much lower number as, unfortunately, we're accustomed to in oncology? And I'll leave it with that. Thank you.

DR. GORMLEY: You raise a good question in that this is a superiority substitution trial, and R-CHOP in and of itself has good activity. And I think that was one of the issues that we tried to highlight in the FDA presentation here, is that we don't know the activity of vincristine, and the activity of vincristine, the regimen that was developed, was not really isolated. Some studies that were done showed a very modest effect of vincristine, but there was no real randomization elaborating the activity of vincristine.

Now we're not suggesting that that should be done but by substituting, then, vincristine for polatuzumab. We're in a situation where we don't

necessarily see a very large robust difference here, and that leads to some questions, then, regarding the efficacy. So I highlight and I agree with your comment, generally, that we are somewhat in a challenging situation regarding, specifically then, what is the contribution and efficacy of polatuzumab in this regimen.

DR. MADAN: Okay. I don't know. It's almost that's more of a question about the vincristine to me, given that that's the standard of care. That's certainly a dimension to this, but it's hard for me to factor that in heavily in this process, but thanks for your time and your answers.

DR. GARCIA: Thank you, all. I know there are a few others raising their hands right now, and perhaps in the interest of time we can take a break. Predictably speaking, we may have a few extra minutes after the break perhaps to address some questions or additional questions that committee members may have for FDA.

We will proceed with a 30-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 resume at 3:36 p.m. exactly. Thank you.

(Whereupon, at 3:07 p.m., a lunch recess was taken.)

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

(3:36 p.m.)

Open Public Hearing

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

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

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

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

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

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

Will speaker number 1 please begin by stating your name and any organization you're

representing for the record?

DR. BAE: Members of the ODAC, thank you for the opportunity to provide public comment today. My name is Richard Bae, and I am a patient living with DLBCL. I want to disclose that I'm also a Genentech employee; however, I am here today to share my views as a patient who received the pola+R-CHP regimen, and I do not represent Genentech.

Before my diagnosis, I was healthy in my 40s, with no significant symptoms, living my life, and I was working at a job that was meaningful to me, socializing with friends, and planning which new country to visit with my husband on our next travel adventure.

Mid last year, I was shocked when I received my diagnosis of stage 4 DLBCL after I found a new primary care physician who took me and my symptoms seriously enough to do more than a routine physical. Upon hearing I had DLBCL, my mind swirled to the worst possible places. How did this happen? What does this mean? My mind went into

problem-solving mode. What treatments are available? Will my insurance cover my treatments? Will the treatment work? Will I live?

I did my research and understood that R-CHOP is the standard of care and would likely be my treatment; however, in speaking with my oncologist, we discussed new data about pola-V, an improved-upon R-CHOP. When I asked her what her thoughts were on the pola-V R-CHP option, she said she was familiar with the data but wanted to dig into it more and consult her colleagues. I left that conversation feeling that I had options whichever direction we went, and that gave me hope.

A few days later, I got a call from my oncologist. She shared that she had read the data and also consulted with other colleagues, and she thought we should try Polivy for me. I asked what changed her mind, and what she said still stays with me. She said, "Richard, I would hate that a few months from now this becomes a standard of care, and I didn't give you the best chance to beat this disease."

From what I understand, there have been many attempts to try to improve upon and better the R-CHOP regimen over the last 20 years, and the pola-V R-CHP regimen has been able to do that. For me, I wanted every bit of advantage I could get to beat my DLBCL from the start.

I recognize how fortunate I was that my oncologist was so experienced with treating patients like me, and that she was also very open to my bringing up new ideas on how I wanted to be treated for my life-threatening disease. It felt like we were sharing this decision together. While she knew about the study and the data about pola-V, she was honest with me that she was not experienced with it but was willing to research and consult her peers to get their perspectives and thoughts. I was lucky that my oncologist was courageous, and humble, and willing to explore and consult others on my behalf to fight for a new option for me, so that I have the best chance to survive my disease and to live.

As a patient that went through the pola-V

R-CHP regimen, I felt the need to come before you all today to share a patient perspective, and to urge you all as advisers to the FDA to please give other patients like me the same opportunity to at least have this conversation with their oncologist about pola-V, to have another option and have another choice at what might be best for them to treat and beat their DLBCL.

Each of you can bring hope for newly diagnosed DLBCL patients so that they can celebrate another birthday like I was able to do recently; or return to work, which I've been able to do after being on disability for almost a year; or to be able to plan for travel again. I urge you all to provide patients a new treatment option that has bettered the standard of care that has helped me to still be here today, and in turn give a ray of light to DLBCL patients when we are thrust into a dark chaotic abyss when we receive our cancer diagnosis.

Thank you very much for your time and your attention.

Clarifying Questions to Presenters (continued)

DR. GARCIA: Thank you, speaker number 1.

It does not appear that we have additional speakers, so the open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience.

Since we have a bit of time left during the afternoon, and I know there were some pending questions from the earlier session, it may be appropriate for us to address some of them. So we can take remaining clarifying questions for all the presenters thus far. Again, please use the raise-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 or end of

your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

So I believe Dr. Sung, Diehl, and Nowakowski, you had some questions that before we couldn't get to. So perhaps we'll start with you, Dr. Sung.

DR. SUNG: Anthony Sung. It was actually addressed by the FDA comments just before the break, so I'm good. Thank you.

DR. GARCIA: Thank you.

Dr. Diehl?

(No response.)

DR. GARCIA: Dr. Diehl, maybe you're on mute.

(No response.)

DR. GARCIA: Alright. Let's just move on.

Dr. Nowakowski, do you have additional comments or questions for the presenters?

DR. NOWAKOWSKI: Thank you, Dr. Garcia, a very brief one.

The protocol allowed prespecified radiation.

Could you just discuss a little bit what are the criteria for prespecifying radiation? Was it for sense of preference or was it more standardized, and what was the use of radiation in both arms?

DR. FUCHS: Of course, Dr. Nowakowski. Let me turn to Dr. Lee to answer your question.

DR. LEE: Calvin Lee with Genentech. The protocol allowed preplanned radiation therapy as determined by the local site investigators. So there was no criteria for radiation therapy as consolidation, such as those with bulky or extra nodal lesions. Out of the patients with predefined radiation therapy, approximately 3-to-4 percent of patients from each arm received preplanned radiation therapy after completion of the study treatment. Thank you.

DR. NOWAKOWSKI: Thank you. This answers my question.

DR. GARCIA: Thank you.

Dr. Diehl, you had a question?

DR. DIEHL: I have a question that perhaps, again, comes from the non-hematologic background.

It's a question maybe for Dr. Flowers and Dr. Friedberg from their clinical expertise perspective.

Dr. Flowers, in your presentation, you were quite eloquent stating, obviously, the statistical difference observed in the POLARIX data, and you stated that the way you explain to patients, and how you interpret and help the patients interpret data is that you have a 25 percent risk reduction of progression relapse or death, translating to an absolute improvement of 5-to-7 percent in PFS at 24 months.

Help me understand how you counsel a patient outside the PFS difference that you observed in the POLARIX data when the R-CHP data did not lead to a mathematical or even a statistical difference in complete responses and/or overall responses; and yet when you look at the survival data as well, although it was not the primary endpoint of the trial, you have a hazard ratio with a medium follow-up of 39.7 months and a hazard ratio with a 95 percent confidence interval of 0.94, but the

confidence intervals are between point 0.67 and 1.33.

So I would translate, as a consumer or a patient, that I could possibly reduce my risk of progression/relapse. I may not have a difference in complete response or overall response, but I have over a 30 percent flat risk of dying on this treatment.

Could you please help me understand that?

DR. FUCHS: Dr. Diehl, I will turn, obviously, to both Dr. Flowers and Dr. Friedberg. I just want to point out, I think with regard to your comment about overall survival just from our standpoint, you're absolutely right. With a hazard ratio of 0.94, which is consistent at multiple time points, the confidence limits are wide, and I think that reflects the fact that even with a 2-to-3 year follow-up, 85 percent, despite even recurrence, are alive, I think which reflects the nature of salvage therapy for this field. I think the precision -- you're right -- around that estimate is wide, but consistently it has a ratio of less

than 1, so there's no empiric evidence that we're seeing of a detriment in overall survival.

But forgive me. I do want to let Dr. Flowers and Dr. Friedberg answer your question.

Dr. Flowers?

DR. FLOWERS: Thank you, Dr. Fuchs.

This is Chris Flowers. If I understand your question, it really centers around some of the endpoints in this study, the progression-free survival, the complete response rate, and the overall survival. As I mentioned in my presentation, really, progression-free survival is a key endpoint for patients with diffuse large B-cell lymphoma because it represents that pathway towards cure with first-line therapy, which is what all patients want and what all providers would like to provide for their patients.

So as I described in my presentation, the ways that I help patients to interpret that is using that 2-year milestone, understanding that the 2-year milestone in and of itself is not the primary benefit of the study; it's progression-free

survival overall. But that 2-year milestone provides a way to conceptualize it for patients, and that, as you mentioned, constitutes a 5-to-7 percent benefit in progression-free survival at 24 months.

The complete response rate data, as you alluded to, in this trial showed a numerically higher complete response rate for the group that received pola+R-CHP but not achieving a statistically significant benefit. That was something that as a steering committee we looked at within the context of this trial, and one of the reasons why we had that lower in terms of the prioritization and not in the hierarchy of testing.

One of the things that we're learning over time is that complete response rate by PET negative by complete response rate may not be equivalent for all complete responses. You see some evidence of this in the trial in that the duration of complete responses for the group that received pola+R-CHP was longer than the group that received complete responses with the R-CHOP regimen, suggesting that

perhaps the depth of complete responses beyond what is measured by a PET-negative CR are actually quite meaningful. And those endpoints had hazard ratios of 0.74 as well, or around that in both the duration of response and disease-free survival.

In terms of overall survival for diffuse large B-cell lymphoma, as I showed in my patient journey, there were many therapies that we can give in the relapse setting. So there are multiple ways that we are able to prolong overall survival, but with the exception of the two curative approaches that I mentioned, those require continuing to give therapy to patients. So the overall survival may not be different in this arm due to those therapies that can be given at subsequent or later lines of therapy, but that clearly requires the toxicity, the hospitalization, and the other untoward adverse events that are needed with second or later lines of therapy.

So really, the goal of first-line therapy is to prevent those events, and that's the way I counsel my patients, is that we want to give the

best and most effective first-line therapy to be able to avoid downstream events.

Dr. Friedberg, was there anything that you wanted to add?

DR. FRIEDBERG: Yes. Jonathan Friedberg.

Thank you, Dr. Fuchs. I agree completely with what Dr. Flowers said and will really just emphasize that what at first seemed somewhat discordant, the CR rate versus PFS, is simply because our ability to measure CR is limited. And what proves that is the fact that one of the problems is that in diffuse large B-cell lymphoma, people go into CR and then they relapse.

So what we're demonstrating here is that even though scans may look similar, we're curing more patients with the pola+R-CHP regimen than we are with the R-CHOP regimen. I think as we look forward to more careful measures of CR with techniques that are still evolving, like circulating tumor DNA and that type of thing, we may have a better way to reconcile those two findings. But since CR is simply defined now based

on PET imaging, I think it shows some of the limitations behind that technique.

I agree completely with the discussion on overall survival. It's not surprising at all at this early time point that we wouldn't see differences. I'm optimistic that we will see differences and, again, I reference the ECHELON trial that took 5 to 6 years for the overall survival signal to emerge in that disease. In large-cell lymphoma, it may take even longer.

DR. GARCIA: Thank you both.

Just an additional question before I move on. Would it be fair to state that when you're talking about we're curing more people with this regimen, you're talking about those patients who achieve a complete response?

DR. FUCHS: Dr. Flowers?

DR. FLOWERS: Thank you, Dr. Fuchs. Chris Flowers here. Really, the landmark that I showed you in progression-free survival at 2 years is the milestone that is most useful for understanding that.

Perhaps if you'll bring up the the slide for the core deck, 17, that I showed in my presentation; the general definition of cure that has been used as having a life expectancy that is similar to age and sex-matched control populations, here, that's what's shown in the orange dotted line.

These are age and sex-matched control populations from a population that is matched to more than 5,800 patients in first-line randomized-controlled trials with R-CHOP. This is the largest study of its kind that was ever performed, and what this shows is those patients that achieved progression-free survival at 24 months, shown in the blue line on the left-hand side, had an overall survival that was similar in life expectancy to the age and sex-matched control general population, which at least in my mind is the definition of cure.

For that patient population, that really is the milestone, and that's the 5-to-7 percent benefit that I described in our population as being

about 25 to 35 of those patients that we see out of 500 patients that we see with diffuse large B-cell, lymphoma at MD Anderson. You see from the curve to the right that those patients who don't achieve that have very different outcomes.

DR. GARCIA: Thank you.

Perhaps we can allow Dr. Kasamon from the FDA to make a comment or a question.

Dr. Kasamon?

DR. KASAMON: Thank you, Dr. Garcia.

This is Yvette Kasamon. FDA would like to make some brief additional comments with respect to the overall survival curve and communicating the results. I'm going to pass it over to Dr. Yazdy. We'd also like to project one of the slides from FDA.

DR. YAZDY: Thanks, Dr. Kasamon.

This is Maryam Yazdy. We thought that it would be very important to again show the overall survival Kaplan-Meier curve for the largest subgroup of this trial; that is the diffuse large B-cell lymphoma and OS that was 84 percent of the

population, 740 patients, because there's uncertainty about the results.

So as you see here, again, the overall survival hazard ratio for this subgroup is 1.02 and an upper bound of 1.49. And if you look at the 1-year overall survival estimate, it is a 91.8 percent in pola+R-CHP versus 95.5 percent in R-CHOP, favoring the R-CHOP arm. Again, we understand the limitations of subgroup analyses, but this an important observation that we have, and there's uncertainty in the point estimates as we see the divide in the confidence interval.

Just to conclude, these results are concerning and they should be considered when you evaluate the risk-benefit of polatuzumab in diffuse large B-cell lymphoma. Thank you.

DR. GORMLEY: This is Nicole Gormley. I'd like to just add, when we are looking at and talking about cure, the endpoint that we have available here is overall survival, and progression-free survival at 24 months was not prespecified in this trial. If it's an endpoint

that the sponsor would like to evaluate, then it should be prespecified in the protocol and SAP.

So I think, again, taking into consideration what we have available to us here from an efficacy standpoint, it's progression-free survival, overall survival, the response rate, overall response rate, and CR rate. So again, those were the prespecified endpoints in this trial.

DR. FUCHS: Dr. Garcia, this is Dr. Fuchs. May I also respond?

DR. GARCIA: Absolutely, Dr. Fuchs. Please go ahead.

DR. FUCHS: Of course. Let me just say we absolutely align with the Food and Drug Administration and that you want to interrogate these databases. Patients depend on us to do that. That being said, the primary endpoint of this trial was progression-free survival. That was done with review with the FDA, and it met its endpoint, which is statistically significant; and I'll turn back to my colleagues, Dr. Flowers and Dr. Friedberg, that we would suggest it's clinically meaningful.

With regard to any individual subset analyses of overall survival, again, on an intent to treat, the hazard ratio is 0.94 consistently at 2 and 3 years, and because the event rates in overall survival are small, when you start to cut the data, the precision in unplanned subset analyses will vary.

Albeit, we have no objection to doing these subsets. I think we have to view them exploratory and, albeit, the slide that's before us is an unplanned subset. You're cutting an event rate where if only 15 percent of patients are having that event, you're then cutting the data in a manner that's hypothesis generating and unplanned, and obviously retrospective, but let me just emphasize.

We are aligned with FDA that we should explore this database, but at the end of the day, the study met its primary endpoint, it's clinically meaningful, and we can't see, by any empiric data on an intent to treat, any decrements in survival. But I think Dr. Flowers also wanted to add

something.

DR. FLOWERS: Thank you, Dr. Fuchs.

Really, just two very quick comments here. First, PFS 24, it's agreed that that was not an endpoint of the study. Progression-free survival was the primary endpoint for the study. PFS 24 is really used as a way to illustrate simply the benefit of PFS, and to be able to explain it in a general context.

I think also the curve that is shown here on overall survival is an important one to think about in terms of the deaths, that 8-to-18 months, and the steering committee asked for deep interrogation of the data there. And maybe I'll turn to Calvin Lee to describe the data between the 8-to-18 months, if you could.

DR. LEE: Thank you. Can we have slide 17 up, please? This is Calvin Lee again.

When looking at the deaths that occurred in that period in the intent-to-treat population, we observed that there were 22 patients and 25 patients, respectively, with deaths between that

period of interest as discussed by our review team. We looked at the specific causes of death, and the majority of these, of course, related to disease progression or progressive disease as outlined here, and then there are also other causes of death.

Now, certainly it is important in the benefit-risk assessment to assess what are the main effects that can be causing deaths in this patient population, and "other" of course is a very vague term, so I'll go to slide 18 that provides the specific information of these deaths that occurred during that period in question. The main areas of late effect or intermediate effect that we might be concerned with R-CHOP are traditionally infection related, organ dysfunction, second malignancies; and within those three main categories, we don't see a pattern of difference between the two arms, suggesting any risk or detriment.

So that's the basis of our interrogation, that we remain very confident that there is not detriment associated with this regimen, and the

benefit seen in the PFS is of importance and not clouded by this overall survival analysis. Thank you.

DR. GORMLEY: This is Nicole Gormley.

DR. GARCIA: Go ahead.

DR. GORMLEY: Thanks for the opportunity. I think we just wanted to comment. Our question's really pertaining to overall survival entirely, the results overall, so that's just one comment.

Then I wanted to just provide a little bit of detail. It was assumed that there would be 178 events overall survival, events at the time of the final analysis, and at this point, there were 131 events observed. So I'm just trying to put that into context, the amount of information that we currently have.

I would just conclude by saying, again, the endpoints that we focused on are the ones prespecified for efficacy and specified in the protocol and the SAP. But overall, we look at the totality of data. We look at the entire information available to us, and that's, again,

what we're seeking the committee's input on today. Thank you.

DR. GARCIA: Thank you, Dr. Gormley.

Dr. Pai, do you have a question?

DR. PAI: Yes. Thank you. Amit Pai. I just want to ask a question related to a question that Dr. Garcia asked at the beginning of this discussion that's safety related.

Looking to the briefing document, looking at the summary of resolutions for the profile of peripheral neuropathy, this is not presented in the slide, I don't think; but what I saw is that the incidence of peripheral neuropathy was around 52 percent in both groups, but the resolution of that adverse event seemed to be higher in the R-CHOP group versus the pola+R-CHP group.

Could the Genentech team please give more information about that difference? Is that difference statistically significant? Just a little more information about why there might be this difference potentially if it's statistically significant.

DR. FUCHS: Dr. Pai, of course. Let me turn to Dr. Lee to answer your questions specifically about peripheral neuropathy.

Dr. Lee, did you want to call up the slide?

DR. LEE: Yes. Could we have the backup to safety, slide 12, up? Thank you.

With respect to peripheral neuropathy, at the time of the primary analysis, there was approximately just under 10 percent difference in terms of resolution of neuropathy experienced in the study from the vincristine arm compared to the polatuzumab vedotin arm.

Here is a different type of schematic showing the incidence of peripheral neuropathy at the different clinical visit, collected in a blinded fashion during the study up to the time of that primary analysis. Here, the main question was does the patient have the adverse event of peripheral neuropathy?

As you can see, during the earlier treatment cycles, specifically cycle 1 through 6, the instance of neuropathy as experienced by the

patients in the R-CHOP arm are approximately 10 percent higher than in the polatuzumab R-CHP arm. Now, what we see in the follow-up period, such as treatment completion and the 12- and 24-month follow-up period, is the incidence of neuropathy is similar between the two treatment arms, albeit this is limited by the number of patients who have reached the clinical visit milestone.

Going to the question of resolution of neuropathy, there is a higher incidence of early onset neuropathy with vincristine that seems to correlate with an earlier resolution of neuropathy in the vincristine arm as compared to the polatuzumab vedotin arm. At the same time, when we look at the updated data set, the majority of the patients with clinically important or more severe neuropathy, specifically grade 2 and above neuropathy, it's similar between the two treatment arms, with approximately 3 and 5 percent, respectively, having grade 2 or above neuropathy at the time of the final cutoff date, which is

significantly lower than the maximum rate, which was 17 and 16 percent experienced at any time point in the study. Thank you.

DR. PAI: Thank you for your response.

DR. GARCIA: Thank you.

Dr. Madan?

DR. MADAN: Yes. Ravi Madan, NCI. Along the lines of toxicity -- I guess this is a question for the sponsor, but if the FDA wants to chime in as well -- for me, the biggest concern and the potential of translating this from a clinical trial setting, which is relatively controlled to the community, if I have this correct, there's a 77 percent increase in febrile neutropenia that increased from 35 patients in the control arm to 62 in the investigational arm.

Can the sponsor provide any ways to allay my concerns about translating this to the community? Although it didn't show up as increased mortality in the study, it may become a problem as you start using this in a less controlled setting. Thank you.

DR. FUCHS: Dr. Madan, I'm going to ask Dr. Lee to answer your question on the specifics of the data within POLARIX, and then also ask Dr. Flowers to offer some additional context with regard to DLBCL treatment.

Dr. Lee?

DR. LEE: Thank you, Dr. Madan. Calvin Lee with Genentech. We did perform additional analyses looking at the incidence of febrile neutropenia. One of those is, did patients receive growth factor prophylaxis every time prior to the febrile neutropenia? In this particular analysis, we did see a slightly higher incidence, but the difference wasn't quite as marked, with 10 percent in the polatuzumab R-CHP arm experiencing febrile neutropenia and 6 percent in the R-CHOP arm experiencing febrile neutropenia in the presence of documented primary growth, G-CSF, prophylaxis prior to that event happening.

Now, the other translation that we focus on is what are the main serious infectious complications associated with it? While the

instance of febrile neutropenia, as you mentioned, is 14 percent and 8 percent in the two arms, the incidence of serious infection was also about 13 and 10 percent observed, meaning there is infectious complications but the rate of infectious deaths was 1.1 percent, 6 patients in R-CHOP arm and 5 patients in the pola+R-CHP arm.

So certainly there is the concern of myelosuppression here, but perhaps I could also pass this to Dr. Flowers to provide clinical context in the translatability of these signals in a broader setting. Thank you.

DR. FLOWERS: Thank you, Dr. Lee. This is Chris Flowers from MD Anderson. Perhaps I'll also allow Dr. Friedberg to comment if he has additional comments, after my comments.

As you heard in my introductory remarks, with the R-CHOP regimen, the kinds of adverse events that have been seen in the management of patients -- febrile neutropenia, neutropenia, and neuropathy -- are the kinds of events that community providers are very comfortable with

managing. As I mentioned, this is a regimen that nearly every community provider is comfortable with giving.

Perhaps one of the things that I'll add there is that as an investigator involved in this double-blind, randomized-controlled trial, many of you who are investigators, who've been involved in randomized trials, know that sometimes you can tell the difference between the arms based on the adverse event profile, and that was not true in this double-blind, randomized-controlled trial. The arms were essentially indistinguishable in terms of their adverse event profile. This is a regimen that is commonly given in community practices, and I would expect the pola+R-CHP regimen to be one that also community providers would be comfortable with giving.

Dr. Friedberg, did you want to add anything?

DR. FRIEDBERG: I've nothing to add. I agree completely with what Dr. Flowers said.

DR. GARCIA: Thank you.

Dr. Nowakowski, you had a question?

DR. NOWAKOWSKI: Yes. Thank you. I have a question to the sponsor; Greg Nowakowski.

DR. GORMLEY: Sorry to interrupt. This is the FDA. Could we respond to that comment first before going to the next one? Is that possible?

DR. NOWAKOWSKI: Sure.

DR. GARCIA: Who is this?

DR. GORMLEY: This was Nicole Gormley. Is it possible for the FDA to respond to that before going to the next question?

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

DR. KASAMON: This is Yvette Kasamon. FDA would like to comment further about the characterization of myelosuppression. I will turn it over to Dr. Yazdy. Also, we like to show the FDA slide, please.

DR. YAZDY: This is Maryam Yazdy. Thank you for your question. We just wanted to add some information about your concern regarding the febrile neutropenia. That is a correct observation. The incidence of neutropenia was similar, but we would like to point out that the

depth of myelosuppression might be underestimated in POLARIX because lab checks were mandated just once per cycle, so it's possible that myelosuppression and neutropenia is underestimated.

I just wanted to add that, as mentioned, febrile neutropenia was 14 percent in the pola arm compared to 8 percent in the R-CHOP arm, and also, infection rate, including grade 3 to 4 infection rate, was higher in the pola arm, but as the applicant mentioned, this did not translate into fatal infection. Thank you.

DR. KASAMON: This is Yvette Kasamon. I just wanted to also add in terms of the schedule of the mandated lab evaluations in POLARIX, as Dr. Yazdy stated, labs were mandated once per cycle, but they were mandated at the start of each cycle. The counts generally dipped days 8 through 15 or so into a cycle, so the mandated lab checks done at the beginning of each cycle are likely missing that nadir. So for that reason, there are uncertainties as to the true depth of myelosuppression in either arm. We also note that

adverse events in the data sets tend to underreport the true incidences of treatment-emergent cytopenia. Thank you.

DR. FUCHS: Dr. Garcia, this is Charlie Fuchs. I wonder could I just turn to Dr. Friedberg just to comment on the -- I think the FDA raises an interesting point about the frequency of checking CBCs.

Dr. Friedberg, did you want to comment on that in the context of practice?

DR. GARCIA: Go ahead.

DR. FRIEDBERG: Thank you, Dr. Fuchs.

I agree with Dr. Kasamon that in the trial, it was not mandated to check CBCs frequently. That is not a standard practice. Generally, we check CBCs before each cycle of treatment. I think the key point where we get concerned about neutropenia in the treatment of diffuse large B-cell lymphoma is that if count recovery does not occur in time to give the next cycle, and you have to delay cycles, that is a sign that you will have an increased risk of failure of the treatment.

In this study, as was shown, the dose intensity of both arms was absolutely equivalent, and there was no indication that there were cycle delays due to prolonged neutropenia in one arm versus the other arm. And I think that's an important point because if the duration of neutropenia were different between the two arms, that difference would be small because we're not seeing any cycle delays. Thank you.

DR. GARCIA: Thank you.

Maybe we have time for one final question, or maybe two now.

Dr. Nowakowski and Dr. Sekeres.

DR. NOWAKOWSKI: Thank you, Dr. Garcia. I'd like to divide this question to the sponsor and to FDA colleagues as well. Let me start with the question to the sponsor part.

If you look at the outcomes of this study and many other randomized studies in large-cell lymphoma, the outcomes, even in a control arm, are way better than what we see in databases or generally in community, and that's obviously driven

in large part by patient selection on those trials.

A colleague of mine, Dr. Khurana, performed a different analysis when she looked at the inclusion criteria in the trial, and applying those inclusion criteria to the general diffuse large B-cell lymphoma population and how many patients would be actually eligible for the trial, in the case of POLARIX, only about 16 percent of the patients would be excluded by laboratory values from the study at the initial diagnosis, and if you look at the patients that represent the minorities, this percentage goes up to 22 percent.

So there's a significant proportion of patients which likely in the community, in the real world, would get treated with this combination, which was not necessarily included in the study, and that's affecting not only this study; that's true across all the studies we've been designing over the years.

My question is, is the sponsor planning on additional studies or safety evaluations of this combination in those patient populations, with all

the dysfunctions and comorbidities, to produce the signal of safety and efficacy?

DR. FUCHS: Dr. Nowakowski, I think you raise a number of interesting points with regard to the nature of patient cohorts enrolled in clinical trials. With regard to other patients that would otherwise have been excluded, we don't have immediate plans to conduct additional studies in individuals who have other comorbidities.

What I would say is, globally, roughly about 3,000 patients have now gotten pola+R-CHP for the treatment of diffuse large B-cell lymphoma based on those other approvals, and with regard to the pharmacovigilance, we're not seeing any new safety signals but, obviously, in the context of hopefully gaining approval for this regimen in the U.S., we're happy to negotiate with the FDA on what additional data they would like.

DR. NOWAKOWSKI: Thank you, Dr. Fuchs. I do encourage the sponsor to do that because it's an unmet medical need, and there are concerns about safety signals in those populations, and we really

have to explore how those populations could be better treated.

The other point moreover is to our colleagues from FDA and the question about the regulatory strategy, and how the decision about this particular approval affects our thinking about the future trials and future landscape of diffuse large B-cell lymphoma.

R-CHOP is truly a standard established on three studies, which you very nicely showed with benefit in overall survival, and has been a standard, as others pointed out, for a very long time. Here we have a study which produces a modest benefit in progression-free survival and the overall survival benefit.

So let's assume if this standard gets approved, how do we consider future studies in this space? Because, for me, based on lack of overall survival, if this was to get approved, this would be more of an option than necessarily a new standard since there's no overall survival of benefit. Hence, R-CHOP would be still a reasonable

option.

This is even reflected -- Dr. Fuchs showed nicely that [indiscernible] has approved or endorsed this combination, but if you look at the countries section, it's highly variable, based on the lack of overall survival benefit. So it becomes more of an option than a standard.

So the question is, would you consider for the future study, designed now or in the future, this to be a new control arm, or would you say, "Well, there's no overall survival difference, and control arms should be R-CHOP or R-CHOP-like combination" to be still acceptable in the control arms? I know it's a loaded question, but I think it might inform how we are thinking about the future of large-cell lymphoma from a broader perspective.

DR. GORMLEY: Hi. This is Nicole Gormley. Thanks for the question. I think in fairness, this is a little bit out of scope, beyond this meeting, but I will just make a general comment that, in general, any FDA-approved therapy that would be

considered reasonable treatment for a U.S. patient population is acceptable to use as a control arm.

DR. NOWAKOWSKI: Thank you.

DR. GARCIA: Thank you, Dr. Gormley.

We have one final question before we move on to our discussion session.

Dr. Sekeres?

DR. SEKERES: Yes. Thank you. Mikkael Sekeres from Miami.

A quick question for you, and I apologize if this was covered earlier. The scans, the CT scans and PET CT scans, were assessed centrally by an independent blinded review committee; correct?

DR. FUCHS: Dr. Lee?

DR. LEE: Hi. Calvin Lee. So the images were collected, and they were assessed up to the treatment completions, actually. Beyond that, because double blinding was maintained, the detection of progression and disease relapse was assessed locally. Thank you.

DR. SEKERES: So there was no central assessment of progression; it was all investigator

assessment of progression?

DR. LEE: Yes, you're correct. And the reason for this is, in coordination, our steering committee and other clinicians felt detection of relapse was appropriate by the investigator. Thank you.

DR. SEKERES: Okay. Thank you.

Questions to the Committee and Discussion

DR. GARCIA: Thank you, all.

The committee will now turns 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 discussions. I would like to remind the public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel.

When I read the first question, I ask voting members and part of the committee to discuss internally. The question reads, discuss the

benefit-risk profile of polatuzumab vedotin-piiq in combination with R-CHP -- rituximab, cyclophosphamide, doxorubicin, and prednisone -- for the proposed patient population with large B-cell lymphoma, LBCL, including patients with diffuse large B-cell lymphoma not otherwise specified and OS, considering the results of the POLARIX trial.

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

(No response.)

DR. GARCIA: If there are no questions or comments concerning the wording of the question, we will now open the question to discussion within the group.

Dr. Cheng?

DR. CHENG: Yes. Thank you. Jon Cheng, industry rep. I appreciate the discussion, and thank you to the sponsor and FDA for bringing this to the committee.

My question is actually to the lymphoma -- so I'm a solid tumor oncologist and

don't necessarily treat lymphoma, but we have a number of lymphoma experts that are invited, so I'm curious and interested. From the ODAC members who treat lymphoma on a regular basis, help me understand progression-free survival and its clinical benefit. I appreciate hazard ratios are difficult to illustrate, so the 2 years, 6.5 percent has been proposed, but I'm interested if lymphoma progression-free survival is viewed in a way that maybe other solid tumors are not.

Then my second part is this. I did note that the NCCN did have this in its current guidelines, so I'm also curious; is that a common viewpoint that progression-free survival, of this magnitude at least, is a desired option for lymphoma treaters?

DR. GARCIA: Maybe Dr. Nowakowski, do you want to take it?

DR. NOWAKOWSKI: Yes, I can take it. Thank you, Dr. Garcia. Greg Nowakowski.

I think this is a great question. It goes back to this risk-benefit, which our colleagues

from FDA are asking about. In general, I would consider gaining progression-free survival as a significant benefit to the patient, and the reason for this, as others alluded to earlier in the presentation, Drs. Friedberg and Flowers, it does reduce the need for subsequent therapies.

If you look at the large-cell lymphoma landscape, those subsequent therapies, number one, are not very effective, unfortunately; and number two, they're frequently very toxic and involved, including cellular therapies and global stem cell transplantation. There's also phenomenon [indiscernible] work; some of the patients with initial relapse may get quite discouraged, and they are actually not even seeking second- or third-line therapy. So in my clinical practice, I would consider gaining progression-free survival a significant benefit.

Now, this has to be weighted against the overall survival results and overall toxicity of the regimen because, obviously, if you had a significant gain in progression-free survival but

therapy was extremely toxic and resulting as deaths or other sustained toxicity, that's not something which we would like to use. And that's why discussion here is really focused on this issue of how this balance of gaining progression-free survival goes against overall survival and toxicity.

What we have seen in this study, I did not necessarily see convincing evidence of excessive toxicity. Maybe there are some concerns about neutropenia, and neutropenic fever, and how those counts were monitored. We looked at some of the concerns of how it would extrapolate to the population which would not necessarily fit their criteria for this study, in which community it could be used.

But to answer your question overall, if the toxicity would not be excessive and there will be no detriment in overall survival, I would see gaining both progression-free survival or event-free survival, and a basic reduction in the number of those treatments, as a potential benefit

to patients in this population.

DR. GARCIA: Great. Thank you.

Just a comment, again, for the malignant voting members of the committee today. It's just hard for me to wrestle with vincristine. One has to wonder, there are other ADCs that are approved in other tumors. Granted, solid tumors are different malignant cases, but it's hard for me to believe that, you know -- predictably speaking, one could say that if you had used vincristine and you just simply add polatuzumab, then you may actually have a significant and perhaps prohibitive issue with would neuropathy.

But it's just hard for me, and I'm wrestling with that. Yes, it's a substitution trial, but I still don't know how this ADC in combination with R-CHOP would have fared against R-CHOP together, and that's what I'm trying to wrestle with.

Perhaps, Dr. Dunleavy, you can actually make your comments, and perhaps include my set of questions as well in the group.

DR. DUNLEAVY: Yes, sure. I just wanted to

comment on the progression-free survival question. I agree with Dr. Nowakowski. In diffuse large B-cell lymphoma, compared to other other lymphomas and certain solid tumors, PFS is a really important endpoint. I would say as well that we talk about the potential to get other therapies that may contribute to no overall survival differences, as we see here with this follow-up, but there are a significant proportion of patients who progress with frontline DLBCL treatment who simply are not eligible to get treatments like CAR-T cell and autotransplant for a variety of reasons, just to emphasize the importance of PFS as an endpoint. Thank you.

If you could repeat your question about vincristine specifically, I'm happy to --

DR. GARCIA: That's ok. Don't worry. Just in the interest of time, maybe we can have Dr. Sekeres make a comment.

Mikkael?

DR. SEKERES: Thank you. Mikkael Sekeres from Miami. I must say I'm usually not a fan of

progression-free survival, and I still struggle with how I would convey meaning of that phrase directly to a patient when consenting a patient to go on to a trial if it's in the absence of some improvement in patient-reported outcomes, and here we do not have any improvement in patient-reported outcomes with this. Part of that is because the sponsor stopped collecting information on PRO when a patient progressed, and we may actually have seen differences in PRO if they had persisted in collecting those instruments.

In this case, it's something where it would take a long time to find a survival advantage, so I'm a little more comfortable with looking at an interim marker of a clinically meaningful benefit. I would have liked to have seen some survival data from the initial trial that got this drug approved, and I am a little encouraged by the fact that the PFS seems to be maintained from year 2 to year 3.

My main issue with this trial is I'm still a little bit stunned about the lack of central confirmation of the diagnosis. I think Dr. Flowers

eloquently explained in the very beginning just how complicated it is to make this diagnosis, particularly now, as diffuse large B-cell lymphoma is a broad-broad category and there are many subtypes, some of whom may benefit from a regimen like this and some of whom may not. So the fact that this wasn't centrally confirmed, and that the scans weren't reviewed centrally either for confirmation of progression -- it's the primary endpoint -- I must say that that stuns me when I heard that.

So my problem with progression-free survival is actually not my usual one in studies like this; I kind of get it for the studies of primary endpoint. My problem with it is I'm not sure I trust who progressed and who didn't, and what their base disease was.

DR. GARCIA: Dr. Sekeres, just to push it back on that because I think it's an important point that you have made repeatedly today, I think the bigger question is, if you don't trust pathology because it wasn't centrally reviewed, are

you suggesting that the PFS difference clearly is statistically significant and meeting the primary endpoint, as the applicant pushed through, is not accurate or perhaps an inaccurate reflection based upon that lack of the pathology review?

DR. SEKERES: I think the primary endpoint may not be accurate. I won't say it isn't accurate. I don't know. It may not be accurate because the scans weren't centrally reviewed. The FDA has brought up the heterogeneity of the diagnosis itself as troublesome for this application. I would add to that some more heterogeneity because we don't know what the diagnoses necessarily were because they weren't reviewed by pathologists with expertise in lymphoma, and I just don't know why there was that oversight with a trial of this importance.

DR. GARCIA: Thank you.

Dr. Vasan?

DR. VASAN: I wanted to ask also the lymphoma doctors -- and just drilling down a little bit on these different disease histologies, the

forest plots had such vastly different responses, and Dr. Sekeres mentioned earlier about high-grade lymphoma, and that R-EPOCH and other more intensified regimens, even though we don't have safety randomized data to show superiority for this regimen, it clearly is something that's given in the United States, and it's something that can be given in the community as well.

I guess for the lymphoma doctors, do you have any issues with this very broad indication of all these large-cell lymphoma subtypes, or are you convinced that we have the proper control arm for this high-grade subset of patients?

DR. GARCIA: Dr. Nowakowski, since you're raising your hand, maybe you can tackle that and also make your comments.

DR. NOWAKOWSKI: Thank you, Dr. Garcia.

Dr. Vasan, this is a very good comment, and I think that's what Dr. Sekeres was alluding to as well, because you do have this mixture of patients, and some of those patients with high-grade lymphoma could have benefited from more intensive

chemotherapy. So there's a question here of were they undertreated with R-CHOP, if you would, because of this diagnosis.

As Drs. Friedberg and Flowers alluded to, they've seen no randomized studies which can guide the therapy in this setting, but there's a lot of evidence, including some guidelines, in general, in patients who'd be candidates for much more escalated therapy in those patients; but particularly with double-hit lymphoma, we would consider escalation of therapy. Dr. Dunleavy made comments as well because he's been actually a pioneer of some of this work, where dose-adjusted EPOCH are in this space.

But the other comment, which I'll make, which reflects what Dr. Flowers mentioned, is that there's a clinical trial and there's real life. We always struggle with adaptability of the clinical trial to real life. I can imagine that the regimens like this, as they're getting approved, they'll be used based on local pathology readout. So at some point, what you're facing with those

trials is the reality of what's being diagnosed outside, where there's a lot of controversy and discrepancy between pathologists. Even between the central pathologists, I can tell you that the best lymphoma pathologists can actually argue frequently about those diagnoses, so that's kind of a moving target.

In the past, in a lot of those studies, we tend to be very restrictive and we want central pathology validation, but what this resulted in is excluding other patients with rapidly progressive disease, and the control arm in those studies was unrealistic and basically over-performing because it took so long for us to centrally confirm it.

What I would agree with Dr. Sekeres here is, basically, it would be nice and reassuring to have a central pathology review, retrospectively, for the diagnosis so we can basically do sensitivity analysis and see the concordance in the study results. But I would say that the real-time central pathology review, in general, in front-line large-cell lymphoma studies is not very visible

because of the delay, which is causing dropoff of a lot of patients who would be potentially eligible for this study but have rapidly progressive disease.

DR. GARCIA: Thank you.

Last comment, Dr. Cheng, before we can move on.

DR. CHENG: Sure. Jon Cheng, industry. Thank you, Dr. Garcia. I just want to follow up on the interesting comment Dr. Sekeres made regarding central review of the progression-free survival endpoint versus investigative review or site review.

I was curious, actually, to the FDA as to if there was an internal discussion as to this because, as I understand it, I don't know the lymphoma area as well, but in solid tumors investigator-assessed PFS and investigator-assessed endpoints for progression-free survival has been, I think, accepted as the primary endpoint rather than requiring blinding in a central review.

So I don't know if the FDA had any thoughts

or comments internally, or if they discussed this point, because oftentimes there is discussion with the sponsor regarding endpoints and on the definition of the endpoints.

DR. GORMLEY: Hi. This is Nicole Gormley FDA.

DR. GARCIA: Go ahead.

DR. GORMLEY: Is it ok, Dr. Garcia, if I comment?

DR. GARCIA: Yes, please. Go ahead.

DR. GORMLEY: Thank you.

Yes, this is a point that we had discussion about, the FDA internally. We often do ask for IRC confirmation of the primary endpoint, and that was something that we pointed out that we did not have in this instance. IRC review was conducted for response rate assessments but not progression, and it would have been helpful to have, even if it wasn't necessarily the primary endpoint, as a sensitivity analysis, but that's not what was done here.

I think there are methods to do central

review versus local review in a more expedient manner such that decisions are made at either enrollment or progression at the investigator site, but then there is still central confirmation of that to allow for confidence in the results, and then evaluating whether or not there's consistency between those results. So that is something that we generally do recommend but, as was mentioned, was not done here, so we don't have that data. Thank you.

DR. GARCIA: Thank you, Dr. Gormley.

Before we move to the next question, if I can probably summarize some of the points made by the committee members. It does sound that the group agrees that the PFS appears to be a valid endpoint, and one that is widely accepted by the malignant hematology community and regional oncologists throughout the United States and throughout the world.

I think how you wrestle with PFS and the likelihood of minimizing subsequent lines of therapy, in my mind, remains to be seen, but it

does appear that the group, at least those with lymphoma expertise, feels that that's a significant benefit for that patient population. I think there were a couple of comments related to perhaps oversights on the trial conduct by Dr. Sekeres related to PROs and how that PFS may lose a little bit of momentum, if you will, just by the lack of PRO differences between the arms. Right now, with the data that we have, it's unknown.

Equally important, as stressed by many people, the lack of central pathology up front perhaps, actually, is not clearly defining pathologically the subset of patients who may benefit the most from this regimen or who may not for that matter; something that may become an issue -- this regimen -- if in fact it moves forward into the community practices across the systems; and certainly, also the heterogeneity of the patients treated in this trial. But I think that for the most part, the group feels that the primary endpoint of PFS was a valid endpoint and is something that is widely adopted.

Let's move on to question number 2. So again, this is a discussion question. I'll read it. Based on the results of the POLARIX trial, specifically the overall survival results, discuss whether additional follow-up data from POLARIX should be required to inform the benefit-risk of polatuzumab vedotin-piiq in patients with large B-cell lymphoma in the frontline setting.

I can open up the the floor for discussion. So I've wrote out this question as to how to interpret that PFS improvement with a lack of statistical difference between complete responses, and duration of response for that matter, and the hazard ratio with a wide confidence interval that really actually crosses 1, and that, again, makes me concern.

But I did hear from you, Dr. Sekeres, that would be a vast difference; that that hazard ratio may not be a difficult point for you when you're conveying this information to patients. Is that something that you believe is the case?

DR. SEKERES: Yes. I've long held this

opinion, and it isn't specific to this trial, but I think PFS in and of itself is a challenging endpoint to convey to patients with how that should be clinically meaningful to them out of the context of something that accurately predicts overall survival or if it has a companion, health-related quality-of-life component to it. In other words, classically it's truncated that regulatory bodies look at lives longer or lives better. PFS doesn't say that a patient lives longer or lives better in the absence of survival or health-related quality of life.

DR. GARCIA: Thank you for that insight.

Anybody in the group want to comment as to the task of talking a little bit about that survival result and whether or not we'd like to see more long-term follow-up data.

Maybe Dr. Diehl?

(No response.)

DR. GARCIA: Dr. Diehl, maybe you're muted.

DR. DIEHL: Can you hear me?

DR. GARCIA: Yes. Please go ahead.

DR. DIEHL: A big point on this trial is kind of exemplified by the ECHELON trial, and the ECHELON was a Hodgkin's trial, which took a long time to come to fruition and show an overall survival.

The difference between this trial and the ECHELON trial, though, is that in the ECHELON trial, we could see the death rate changing, and the delta of the death rate changing, with every subsequent publication. In this trial, the death rate appears to be virtually exactly the same, and as I looked at those curves, consistently staying exactly the same.

So my question is, have we done a futility analysis or a projection that given the 10-year follow-up number that was mentioned, we will see a survival difference?

DR. GARCIA: Does anybody on the committee want to address that's comment?

Dr. Nowakowski?

(No response.)

DR. GARCIA: Dr. Conaway, let's go with you

if Dr. Nowakowski is having technical issues.

DR. CONAWAY: Yes. I had exactly the same question as Dr. Diehl. We heard that it will take 10 years of follow-up, or whatever, but that's kind of a general statement about these trials in general. That was just in question; were there any projections about what are the chances we will see an overall survival difference in an additional 1-year, 2-year, 3-year, 4 years of follow-up?

DR. GARCIA: Well, I would argue that the data --

DR. NOWAKOWSKI: This is --

(Crosstalk.)

DR. GARCIA: Go ahead.

DR. NOWAKOWSKI: Sorry. Greg Nowakowski. Sorry for that technical difficulty. Maybe I'll comment. This will likely require some formal statistical modeling, and obviously they've been asked to adapt that, so I don't know if such an effort is being made.

In general, if you look at large-cell lymphoma -- and Dr. Flowers showed it in his

talk -- the patients who do not relapse within 24 months, even if they had relapsed later on, for those stations as a whole, as a whole cohort, the survival is actually matching the normal survival within a population. That's a very important point because it shows you that those late relapses which happened are unlikely to affect the overall survival. So definitely the relapses after 24 months would be quite quite unlikely to contribute significantly to those overall survival curves, and what happens at the time, the mortality from other causes, rather than lymphoma specific, is actually much higher than actually from the lymphoma relapse, so this was a valid observation.

But what brings the issue with this trial is what we have seen here is that the primary factor, the patients were really doing poorly with survival, about 32 to 40 percent, and those will be the ones who didn't achieve complete response and progressed during the therapy or relapsed very early on and were not really affected in this regimen, by use of this regimen. The benefit in

PFS appears to be rising later on.

Now, is this PFS later on clinically meaningful? I believe so because it reduces the need for subsequent therapies, and we had this discussion earlier on. But I think it's going to be more difficult, even with much longer follow-up, to actually show this progression-free survival benefit translates to overall survival just because those later relapses tend to do well with salvage therapies as well.

DR. GARCIA: Thank you.

Dr. Sung?

DR. KASAMON: I'm sorry to interrupt. This is Yvette Kasamon.

Dr. Garcia, may FDA comment, please?

DR. GARCIA: If you can be concise so the panel members can continue discussing internally, that would be great, but please go ahead.

DR. KASAMON: Thank you. I'm going to turn it over to my statistical colleagues.

DR. GU: Hi. This is Wenjuan Gu, statistical reviewer. The applicant provided

calculations that assume a hazard 3.8, 631 events, would be needed to achieve 80 percent power, which is a hypothetical number of events because the applicant's calculations indicate that patients could not be followed long enough to observe this number of events. Using 631 as a benchmark, the 131 events observed at the final analysis corresponds to 21 percent information fraction, which is considered low. Additional OS data would increase the information fraction and improve the precision of the OS hazard ratio estimate.

The applicant provided projections that in the year 2024, two years after the final analysis, 65 more events would likely occur, which is a 31 percent information fraction. Observing at least two additional years of data would improve the precision of the OS hazard ratio estimate, but the applicant's calculations indicate that it's unlikely that the resulting confidence intervals would indicate enough benefit in survival to exceed 1. While it's not necessary to demonstrate statistical superiority and improvement in the

precision of the OS hazard ratio estimate, it would better inform the overall assessment of safety and benefit-risk. Thank you.

DR. GARCIA: Thank you.

DR. GORMLEY: Dr. Sung?

DR. SUNG: Anthony Sung. If I understand the FDA statistician's comment, it sounds like it would be very unlikely to see a statistical difference in overall survival even if followed for 10 years, and I would say, clinically, I would probably feel the same way. We have so many new salvage therapies for lymphoma with CAR-T and everything else, that I don't necessarily think, even if we followed these patients for 10 years, we would see a difference in overall survival.

I think the importance of this drug, what Dr. Flowers and others have been saying, is that as frontline therapy, if we can cure more patients, that's a win. I agree with Dr. Sekeres that it would be great to have more quality-of-life and PRO data, but I think if we can say to our patients, "Hey, you have a greater chance of being cured with

this regimen," I think many patients would take it, and I think as a provider, I would prescribe it.

In terms of the duration of follow-up, which is the the question posed to ODAC here, looking at the PFS curves, they do continue to decline, and I think in general we typically will say when we're looking for a cure maybe looking around the 5-year mark. So if the question posed to the committee is for a number, I would say maybe 5 years, are we seeing differences persistent with PFS? Are we seeing more cures with this therapy?

DR. GARCIA: Thanks, Dr. Sung. But you stated quite eloquently that even with 5 years, it doesn't seem that we're going to even -- if I understood, again, the FDA, their comment, it doesn't even appear that in 5 years we can achieve the same because in 2024, if you go from 21 percent information to 31 percent, with 65 more events, it may not actually lead to that statistical difference that may make you confident that the regimen is not causing detrimental survival for those patients.

Dr. Coffey?

DR. COFFEY: Just to build on that, I wanted to comment. Going from 21 percent information to 33 percent information is going to have very little impact on significance. I think that was kind of implied but not clear; and there was a question earlier on, which is what I originally wanted, about how you would try to project how many you would need. That works better if there's some trend that you've observed and you want to say if this trend persists over time, when would we get definitive evidence? There is no trend here, so no matter what you do, it's going to be heavily driven by assumptions.

So I think this has been said, and by the time I'm speaking, I concur. I think it would be good to get more data. It's the word "required" that I would have more of the problem with because I don't feel like that data is going -- you'd have a more precise estimate but probably the exact same global information at that point.

DR. GARCIA: Got it. Thank you.

Dr. Madan?

DR. MADAN: This is Ravi Madan from the NCI. It's a funny question. I think more survival data is valuable. I think it's in the interest of the sponsor to share that, not just for transparency and clarity, but just to convince the community that they should be using this regimen if it does actually get approved because there's going to be resistance to change out there.

So yes, I think more survival data is valuable to share, and I'm hoping the sponsor seizes as an incentive to get people to use it and build confidence in this regimen.

DR. GARCIA: Thank you.

That sounds that we all agree that -- just to summarize the theme, we do agree that it would be ideal to have additional survival data, but clearly it appears that statistically, it's not going to be feasible or practical to get there in the next 5 or 10 years, just by virtue of the amount of therapies that we have and will likely have in the relapse setting. I like the statement

that Dr. Sekeres made, which is live longer or live better. That doesn't actually reflect, really, a PFS difference, and with the lack of PROS, again, it's going to be very challenging for us to understand what that means.

So I think that, yes, we will likely see survival data, more data about it, but it doesn't seem that it's going to be feasible, based upon the statistical design of the trial. I'm not sure that the question for us as the committee is to really try to understand whether or not the community will buy into the regimen or not, but rather whether or not the data, as we see it, is really actually meeting the statistical endpoints, and therefore becoming clinically meaningful for the patient population in need of this regimen.

In the interest of time, it's around 4:56. Maybe we can move on to question number 3, which is a voting question.

DR. JANKOWSKI: Thank you, Dr. Garcia.

DR. GARCIA: Yes?

DR. JANKOWSKI: Thank you.

DR. GARCIA: Dr. She-Chia Jankowski will provide the instructions for the voting.

DR. JANKOWSKI: Thank you so much.

Question 3 is a voting question. Voting members will use the Adobe Connect platform to submit their votes for this meeting. After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

If you are a voting member, you will be moved to a breakout room. A new display will appear where you can submit your vote. There will be no discussion in the breakout room. You should select the radio button that is the round circular button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected. Please note that you do not need to submit or send your vote. Again, you need only to select the radio button that corresponds to your vote. You will have the opportunity to change your vote until the vote is announced as closed.

Once all voting members have selected their vote, I will announce that the vote is closed.

Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Next, 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 a 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. JANKOWSKI: Dr. Garcia, it looks like Dr. Pai has a question.

DR. GARCIA: Go ahead, Dr. Pai.

DR. PAI: Yes. I just have a quick question about this voting question. Obviously, at the beginning of all of this presentation, the question was that the sponsor was looking for this drug to receive first-line indication, but then this voting question is just asking kind of a generic question about favorable risk-benefit.

In our decision, are we kind of thinking about this compound potentially replacing that regimen or what's the frame?

DR. JANKOWSKI: Go ahead.

DR. GARCIA: I can let the FDA make a comment if the FDA wants to make a concise comment, or otherwise I can just state it myself.

I think the question, to me, is clear. I think that based upon the data that we have in front of us, whether or not we believe that the benefit-risk profile, based on the POLARIX data, for the patient population is favorable or not. Independent of what happens with the regimen, whether it gets approved or not, it's just based upon the data that we have in front of us.

But I always believed that you cannot make these decisions in a vacuum. You have to really understand what the landscape is in the frontline setting for patients with untreated diffuse large B-cell lymphoma NOS or large B-cell lymphoma, and you also have to actually recognize what is the sequence of events that happen after you get

therapy and you relapse or progress.

So I think the bigger question is, with the POLARIX data, do we believe the benefit that was seen with the endpoint demonstrated in that trial against the risk profile, against the patient population in the context of untreated patients, if we believe that regimen actually has a favorable benefit-risk.

DR. PAI. Okay. Thank you.

So I will read the question again. Again, this is a voting question.

Given the results of the POLARIX trial, does polatuzumab vedotin-piiq have a favorable benefit-risk profile in patients with previously untreated large B-cell lymphoma, including diffuse large B-cell lymphoma NOS?

If there are no questions or comments concerning the wording of the question, we will now begin the voting on question number 3.

DR. JANKOWSKI: Thank you, Dr. Garcia.

We will now move voting members to the breakout room to vote only. There will be no

discussion in the voting breakout room.

(Voting.)

DR. JANKOWSKI: Voting has closed and is now complete. Once the vote results display, I will read the vote results into the record.

(Pause.)

DR. JANKOWSKI: Voting has closed and is now complete. The vote results are displayed. I will read the vote totals into the record. There are a total of 11 yeses, 2 noes, and zero abstentions. The chairperson will go down the list, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to. Thank you.

DR. GARCIA: Thank you.

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

We'll start with Dr. Pai.

DR. PAI: Amit Pai. I voted yes. I didn't see any increased risk of toxicity with this

compound and potential benefits in year 2 to 3. Thank you.

DR. GARCIA: Dr. Sung?

DR. SUNG: Anthony Sung. I voted yes. This is a randomized clinical trial that met its primary endpoint of improvement in progression-free survival. I think that this is a clinically significant endpoint, and I feel that the difference, even though it is small, is statistically significant and clinically significant as well. And as Dr. Pai has stated, the risks are reasonable, and the side effects and certain toxicities are reasonable. Thank you.

DR. GARCIA: Thank you.

Dr. Coffey?

DR. COFFEY: Christopher Coffey. Yes, and essentially for the reasons that the prior two stated.

DR. GARCIA: Thank you.

Dr. Nowakowski?

DR. NOWAKOWSKI: Greg Nowakowski. I voted yes because I do believe that this gain in

progression-free survival is clinically meaningful for patients and also leads to reduction in the need of subsequent therapies, and there was no adverse major toxicity signals, which would have been detrimental in this study.

I would like to note, however, that I would consider this regimen to be an option rather than a standard. In a setting of lack of overall survival difference from R-CHOP, I would consider them equivalent, including in ongoing clinical trials, I would not hesitate to randomize patients to the R-CHOP control because there's no overall survival difference. In the future as well, unless a future overall survival difference is shown for this regimen, I would consider them to be a choice rather than a new standard for pola-V R-CHP.

DR. GARCIA: Thank you.

Jorge Garcia. I voted yes. I think with the complexity of our discussions today, I think that the trial met its primary endpoint. I was convinced by what I heard today from the speakers and within our group, in the voting committee

group, that PFS in this patient population is an accepted endpoint for everybody who sees these patients. And although I continue to wrestle with that lack of difference in complete responses and the existing survival data, it appears to be impractical for us to wait for that final OS that may never arrive based upon the inability to get there.

I also was convinced that reduction in subsequent treatments when patients relapse is critically important as well. So for that reason, I voted yes.

Dr. Dunleavy?

DR. DUNLEAVY: I voted yes. I believe progression-free survival is very meaningful endpoint in diffuse large B-cell lymphoma, and the results here are clinically meaningful, as also evidenced by the reduction in subsequent therapies and the maintenance of PFS with longer follow-up.

I do agree with Dr. Nowakowski. I do think that this should be an option for patients. There is slightly increased toxicity, and I think it's

going to be very important to assess this in a less controlled setting in the real world to see the differences in efficacy and toxicity in a non-controlled population.

DR. GARCIA: Thank you.

Dr. Diehl?

DR. DIEHL: Lou Diehl, and I voted yes. I'm going to say much the same thing perhaps in a little different way. Progression-free survival in and of itself has no particular value. It is a surrogate endpoint. It gets its value because it demonstrates an improvement in overall survival or an improvement of quality of life, neither of which we have here. So we go to a secondary endpoint, a surrogate endpoint, and that is toxicity of the regimen.

I do think the fact that the control group, the R-CHOP group, is going to have to have more CAR-T and more transplant, that they are going to have more toxicity, and that's what I see this drug regimen preventing, and that's why I voted yes.

DR. GARCIA: Thank you.

Dr. Conaway?

DR. CONAWAY: Yes. Mark Conaway. Even though I agree that pola+R-CHP did show benefits in this trial, for me at present, there was just too much uncertainty about the magnitude and robustness of the treatment effects.

DR. GARCIA: Thank you.

Dr. Sekeres?

DR. SEKERES: Yes. Mikkael Sekeres, and I voted no. I felt as if this trial didn't meet the basics of a large clinical trial in hematologic malignancies, and there wasn't confirmation of the diagnosis, and there wasn't confirmation of whether or not patients actually progressed before they were removed from the trial.

Progression-free survival in and of itself, in a disease that has comparatively lower mortality rate and in whom people live for a while, I think is ok as long as it has supportive data, but I couldn't even trust whether or not patients truly progressed on this study.

DR. GARCIA: Thank you.

Dr. Vasan?

DR. VASAN: Neil Vasan. I voted yes. This trial did meet its primary endpoint of PFS, and while there was a lack of congruence among the prespecified endpoint, I believe the benefits outweigh the risks and that polatuzumab vedotin should be an option for first-line treatment of DLBCL with curative intent, especially noting, as was previously discussed, that patients would be spared more toxic and complicated salvage therapies. Thank you.

DR. GARCIA: Thank you.

Mr. Majkowski?

MR. MAJKOWSKI: Yes. Paul Majkowski, patient representative. I voted yes. In terms of weighing benefits and risks, repeating what's been said, it seemed really in my mind, too, the primary benefits, the increase in progression-free survival, while modest was an improvement over R-CHOP. It also stuck out to me significantly that the data showing stem cell transplants and CAR-T therapy were cut in half.

On the risk side of the ledger from the patient perspective, I think that one of the things you would not want to be in the situation of would be thinking did I choose wrong if there were different options, and I think that's where some of the similarity between the treatments and, really -- and perhaps this is not entirely scientific, but the regimens are you're still maintaining the Rituxan and the other agents. So I didn't see where there was a risk that would outweigh those benefits. Thank you.

DR. GARCIA: Thank you.

Dr. Madan?

DR. MADAN: Yes. Ravi Madan, NCI. I voted yes. The question today before the committee relates to improving on a very effective standard of care in large B-cell lymphoma. Historically, R-CHOP has been a regimen that has been very hard to improve on largely because of its roughly 70 percent efficacy rate. The data reviewed today with R-CHP and polatuzumab does meet its endpoint PFS relative to R-CHOP, and while PFS is not always

meaningful, in this case I think it is.

While the data is not as robust as we're used to seeing in oncology settings, I'm not convinced that you can have a robust improvement on a highly effective regimen such as R-CHOP without designing an impractically large study. I understand the FDA is concerned about overall survival, but those timelines seemed too protracted to evaluate in a meaningful way. I do have concerns about the increased risk of febrile neutropenia, but it is not a novel toxicity, and I'm optimistic that the community can deal with that effectively.

In the end, if there are going to be improvements in the care of large B-cell lymphoma patients, it may need to start with seemingly small incremental but clinically meaningful and statistically significant steps such as this. Thank you.

DR. GARCIA: Thank you, Ravi.

Dr. Finestone?

(No response.)

DR. GARCIA: Dr. Finestone?

(No response.)

DR. GARCIA: Dr. Finestone, are you mute?

(No response.)

DR. GARCIA: While we sort out those potential issues with her, Dr. Dunleavy, may I ask you please to state your name and vote for the record again, please? It was not captured before.

DR. DUNLEAVY Yes, sure. Kieron Dunleavy. Yes.

DR. GARCIA: Thank you.

Dr. Finestone?

(No response.)

DR. GARCIA: Dr. Jankowski, do we have any technical issues with Dr. Finestone?

(No response.)

DR. GARCIA: Dr. Jankowski?

DR. JANKOWSKI: Thank you. Sorry. I'm muted myself, too.

Thank you, Dr. Garcia. We're checking on her.

Dr. Finestone, can you unmute? Do you have

any technical issues that perhaps we can work with? Thank you.

(Pause.)

DR. JANKOWSKI: This is She-Chia Jankowski, the DFO. Thank you all for waiting. Just give us a few minutes, and we'll try to figure out with Dr. Finestone. Thank you for your patience.

DR. GARCIA: Thank you.

(Pause.)

DR. GARCIA: Three years of COVID, and we still have yet to perfect our technical challenges, all of us.

(Pause.)

DR. GARCIA: We won't be able to proceed until we get Dr. Finestone back on the line so she can vote on the record, so thank you for your patience.

(Pause.)

DR. JANKOWSKI: This is She-Chia, the DFO. I apologize for the delay. I just want to let you know that Dr. Finestone is reconnecting to the audio, so thank you for your patience. Again, I

sincerely apologize for the wait. Thank you.

(Pause.)

DR. GARCIA: This is Jorge Garcia. I'm going to go ahead and summarize our voting while Dr. Finestone connects.

Just to start with the noes, the theme for our two members who voted against basically related to the lack of a meaningful and/or robust difference in PFS. There were comments related to the trial not meeting basic things such as histological confirmation and also central confirmation of progressive disease. Again, although PFS appears to be important for some, the lack of supplemental data related to PROs or OS survival didn't make it that strong.

For the group who voted yes, it seems that we all felt that the primary endpoint of the trial, as it is, was met although the difference statistically may not be mathematically large, but certainly a good way to begin changing the standards for this patient population.

It was also encouraging to see that the

benefit of that PFS was maintained beyond month 24 into the 36-month mark and also comments related to the lack of significant toxicities and perhaps no difference between R-CHOP and polatuzumab in combination with R-CHP. Also equally important, a lot of weight was placed on the reduction in subsequent therapy for those patients who are getting polatuzumab in combination with R-CHP compared to those who have received R-CHOP-based therapy.

Dr. Jankowski, is Dr. Finestone back on the line?

DR. JANKOWSKI: Hi. Thank you, Dr. Garcia. I apologize. We're still working on it. Please give us just one minute. Thank you so much.

(Pause.)

DR. SUNG: This is Anthony Sung. While we're waiting, can I make a comment, or since I already spoke, am I not allowed to?

DR. GARCIA: A comment related to your vote?

DR. SUNG: Yes, and the subsequent vote.

DR. GARCIA: Sure. Go ahead.

DR. SUNG: Thank you.

Again, my name is Anthony Sung. I heard other members give weight to the decreasing number of patients going to CAR-T and stem cell transplant. Actually, that was not significant in my mind. As FDA mentioned, there are a number of factors that could be related to this. You could have a therapy which resulted in patients who are too deconditioned to go on to subsequent transplant, and that's why fewer patients went to transplant.

There was an unplanned post hoc analysis, and I don't think we can necessarily rely or trust that this therapy will reduce the need for subsequent transplant or CAR-T therapy; however, I still vote yes for the reasons I stated previously.

DR. GARCIA: Thank you for your thoughtful comment.

DR. JANKOWSKI: Thank you all for your patience. Since we still continue to have technical difficulty, again, this is She-Chia Jankowski, the DFO. I'm going to state for the

record, for Dr. Sandra Finestone, Dr. Sandra Finestone voted yes for the record.

DR. JANKOWSKI: Handing it to you, Dr. Garcia. Thank you.

DR. GARCIA: Thank you, Dr. Jankowski.

I have already provided a summary as to the themes that supported the vote yes and also the themes that supported the vote no.

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

DR. GORMLEY: I'd like to just thank the committee for your comments, and thank you for [indiscernible] the meeting.

Adjournment

DR. GARCIA: Thank you, Dr. Gormley.

As the chairperson, I'd like to thank all the participants in the meeting. The presentations were outstanding from both the FDA and the applicant. I appreciate the candor, the openness, and the active discussion that we had within the ODAC committee members, so thank you very much to all for your participation.

We will now adjourn the meeting. Thank you, and have a great night.

(Whereupon, at 5:24 p.m., the meeting was adjourned.)