FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Virtual Meeting

Thursday, November 16, 2023

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

Meeting Roster

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Moon Hee V. Choi, PharmD

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Office of Executive Programs, CDER, FDA

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

DR. CHEN: Good morning, and welcome. I would first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Lauren-Jei McCarthy. Her contact information is currently displayed.

My name is Dr. Andy Chen, and I will be chairing this meeting. I will now call the November 16, 2023 Oncologic Drugs Advisory Committee meeting to order. Dr. Moon Hee Choi is the acting designated federal officer for this meeting and will begin with the introductions.

Introduction of Committee

DR. CHOI: Good morning. My name is Moon Hee Choi, and I am the acting designated federal officer for this meeting. When I call your name, please turn on your camera, unmute, and introduce yourself by stating your name and affiliation for the record. We will first start with the standing

committee members.

Dr. Advani?

DR. ADVANI: Ranjana Advani from Stanford.

DR. CHOI: Dr. Choueiri?

DR. CHOUEIRI: Toni Choueiri, Dana-Farber Cancer Institute, Boston.

DR. CHOI: Dr. Conaway?

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

DR. CHOI: Dr. Gradishar?

DR. GRADISHAR: Bill Gradishar, Northwestern University, Chicago.

DR. CHOI: Dr. Lieu?

DR. LIEU: Good morning, everybody. I'm Chris Lieu. I'm a GI medical oncologist from the University of Colorado Cancer Center.

DR. CHOI: Dr. [Mr. - sic] Mitchell?

MR. MITCHELL: I am David Mitchell. I'm not a doctor. I'm the consumer representative to the ODAC. I am the founder of Patients for Affordable Drugs, and I'm a cancer patient.

DR. CHOI: Thank you.

Dr. Nieva?

DR. NIEVA: Hi. I'm George Nieva, Section Head of Solid Tumors, University of Southern California, Norris Comprehensive Cancer Center.

DR. CHOI: Thank you.

Dr. Rosko?

DR. ROSKO: Ashley Rosko, Division of Hematology and medical director of the oncogeriatric program, James Comprehensive Cancer Center, The Ohio State University.

DR. CHOI: Dr. Spratt?

DR. SPRATT: Daniel Spratt. I'm the chairman of Radiation Oncology at UH Seidman Cancer Center and Case Western Reserve University in Cleveland.

DR. CHOI: Dr. Cheng?

DR. CHENG: Good morning. I'm Jon Cheng. I'm the industry representative, a medical oncologist by background, and I'm with Bristol-Myers Squibb.

DR. CHOI: Thank you.

Dr. Chen?

DR. CHEN: Dr. Andy Chen, Knight Cancer Institute, Oregon Health & Science University.

DR. CHOI: Dr. Thanarajasingam?

DR. THANARAJASINGAM: Hi. I'm Gita Thanarajasingam. I'm a lymphoma hematologist at the Mayo Lymphoma Group at Mayo Clinic in Rochester, Minnesota, and a health outcomes researcher focused on cancer treatment, toxicity, and tolerability.

DR. CHOI: Dr. Vinks?

DR. VINKS: Good morning. I'm Alexander Vinks. I'm a clinical pharmacologist and professor emeritus at the University of Cincinnati and Cincinnati Children's Hospital Medical Center. I'm also a partner with NDA Partners.

DR. CHOI: Mr. Zavadowski?

MR. ZAVADOWSKI: Hello. Good morning. My name is Rich Zavadowski, the patient representative, and I am a 15-year survivor of stage 4 peripheral T-cell lymphoma NOS. I was treated and cured at the clinical research program at the National Institute of Health NCI in 2008

when I was 65 years of age. I was treated with EPOCH with [indiscernible], and I had two other non-blood cancers plus a meningioma. I'm an ambassador for the Lymphoma Research Foundation and a patient advocate of the Leukemia and Lymphoma Society.

DR. CHOI: Thank you.

Dr. Pazdur?

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

DR. CHOI: Dr. Theoret?

DR. THEORET: Yes. Hi. My name is Marc Theoret, and I'm a hematologist/oncologist, a deputy director of the Oncology Center of Excellence, as well as an acting supervisory associate director of the Office of Oncologic Diseases.

DR. CHOI: Thank you.

Dr. Kluetz?

DR. KLUETZ: Good morning. I'm Paul Kluetz. I'm a medical oncologist, deputy director of the

Oncology Center of Excellence, and acting supervisory associate director for Cell Tumor Oncology in the Office of Oncologic Diseases in CDER.

DR. CHOI: Dr. Gormley?

DR. GORMLEY: Hi. I'm Dr. Nicole Gormley. I'm the director of the Division of Hematologic Malignancies II and also the acting associate director for Endpoint Development within the Oncology Center of Excellence.

DR. CHOI: Dr. Richardson?

DR. RICHARDSON: Hi. I'm Nicholas Richardson. I'm the deputy division director for the Division of Hematologic Malignancies II. We oversee the development of products for patients with lymphoma, CLL, and multiple myeloma.

DR. CHOI: Dr. Kasamon?

DR. KASAMON: Hi. I'm Yvette Kasamon. I'm the clinical team leader in FDA's Division of Hematologic Malignancies II.

DR. CHOI: Thank you.

Dr. Mehta?

DR. MEHTA: Hi. I'm Gautam Mehta. I'm a clinical team leader in the Division of Oncology II and the project lead for the Oncology Center of Excellence's Project Confirm.

DR. CHOI: Thank you.

DR. CHEN: 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 chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are

anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

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

Conflict of Interest Statement

DR. CHOI: 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 of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not

limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

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

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of

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

For today's discussion, the committee will receive updates on the accelerated approval program in oncology and two new drug applications, NDAs, approved under 21 CFR 314.500, subpart H, accelerated approval regulations, that have not met their agreed-upon milestone for completion of confirmatory trials.

Confirmatory trials are postmarketing studies to verify and describe the clinical benefit of a drug after it receives accelerated approval. These updates will provide information on the status of all accelerated approvals granted in oncology, including products with delayed confirmatory trials and the status of confirmatory trials for the specific NDAs to be discussed, including any ongoing and planned trials.

The two products to be discussed are, 1) Folotyn, also known as pralatrexate, NDA 022468, submitted by Acrotech Biopharma, indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma, PTCL; and 2) Beleodaq, also known as belinostat, NDA 206256, submitted by Acrotech Biopharma, indicated for the treatment of patients with relapsed or refractory PTCL.

Based on the updates provided, the committee will have a general discussion about delayed confirmatory trials, as well as a focused discussion on next steps with two products, Folotyn, also known as pralatrexate, and Beleodaq, also known as belinostat, approved for PTCL. The overall goal will be the continued optimization of the accelerated approval process with a focus on decreasing the amount of time to verify, or fail to verify, clinical benefit while continuing to provide early availability of promising oncology products. This is a particular matters meeting during which specific matters related to Acrotech Biopharma's NDAs will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. Gita Thanarajasingam. Dr. Thanarajasingam's waiver involves nine of her employer's research contracts. The contracts are for various studies funded by competing firms or competing entities. Her employer receives between $0 and $500,000 for four total studies from Effector, Celgene, Daiichi Sankyo, and Aptose; between $50,000 and $100,000 for one study from Shanghai Hai He; between $100,000 and $300,000 for one study from Seattle Genetics; between $300,000 and $500,000 for two total studies from Actuate Therapeutics and a competing firm; and between $500,000 and $700,000 for one study from the National Institutes of Health's National Cancer Institute.

The waiver allows this individual to participate fully in today's deliberations. FDA's reasons for issuing the waiver are described in the waiver document, which is posted on FDA's website

on the advisory committee meeting webpage, which can be found at www.fda.gov and by searching on November 16, 2023 ODAC. Copies of the waiver may also be obtained by submitting a written request to the agency's Freedom of Information Division at 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the products 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 committees of any financial relationships that they may have with the firm at issue. Thank you.

DR. CHEN: We will now proceed with FDA opening remarks from Dr. Gautam Mehta.

FDA Opening Remarks - Gautam Mehta

DR. MEHTA: Thank you, Dr. Chen.

Good morning. My name is Gautam Mehta. I'm a tumor neurosurgeon and acting team lead in the Office of Oncologic Diseases at FDA, and the project lead for the Oncology Center of Excellence's Project Confirm, whose charge is to increase the transparency of the accelerated approval program for oncology indications. To date, FDA's accelerated approval has been used most commonly in oncology, and today I'll be providing

background on the program and will focus on the timely completion of confirmatory trials after accelerated approval, which is the overarching topic of today's advisory committee meeting.

The accelerated approval program is dynamic and has adapted to a rapidly changing cancer treatment landscape over the past three decades. As we continue to learn from our experience and through discussions such as today's, we hope to continue to leverage the benefits of this program for patients with cancer, while minimizing its risks.

In covering this topic, I will discuss some of the risks and implications of delayed confirmatory trials after accelerated approval. I'll cover some of the causes of delays, and finally, I'll go over some strategies to minimize the risk. To give this topic further context and immediate relevance, you'll also be hearing later today from both FDA and the sponsor about two products which have been granted accelerated approval and have delayed confirmatory trials,

pralatrexate and belinostat, both indicated for peripheral T-cell lymphoma.

In this first presentation, we'll establish two key points. First, that accelerated approval provides earlier access to life-saving drugs for patients with cancer but is associated with an inherent period of vulnerability after the accelerated approval is granted and before clinical benefit is verified by confirmatory trials. And what I mean by this period of vulnerability is that this is a period of time where there's a possibility that a drug that may not confer clinical benefit is on the market, and the second key point is that reducing this period of vulnerability is best done prospectively through a comprehensive development strategy with rational data-driven timelines, and we'll discuss some strategies to approach this today.

To start, we need to first review the accelerated approval program. This program was developed in 1992 as a response to the HIV and AIDS crisis, and this approval pathway provides earlier

access to drugs by specifically relying on either surrogate or early clinical endpoints that are considered reasonably likely to predict clinical benefit. In oncology, for example, we've frequently relied on the early clinical endpoint of overall response rate to support accelerated approval. Unlike traditional approval, which purely balances benefit against risk, with accelerated approval, this effect on the early clinical endpoint is balanced against some uncertainty that the drug may not provide clinical benefit.

The way we eventually prove or verify clinical benefit after an accelerated approval is through confirmatory trials. These confirmatory trials are typically underway at the time of accelerated approval and rely on endpoints that are direct measures of clinical benefit such as overall survival. Based on the results of these trials, the indication is either granted a traditional approval or may be potentially withdrawn.

Because it's important for context for

today's discussion, I'll briefly review in what situations FDA will actually withdraw an accelerated approval. First, if the confirmatory trial fails to verify clinical benefit, the accelerated approval may be withdrawn. Next, if other evidence demonstrates that the product is unsafe or ineffective, the drug may be withdrawn

It is important to understand that after a confirmatory trial does not meet its primary endpoint, this regulatory decision to withdraw an accelerate approval is not automatic. This decision is affected by a variety of factors, including, of course, the results of the confirmatory trial.

For example, if the results of the trial are equivocal, this does not necessarily mean that the drug is ineffective or unsafe. In this situation, we'll reassess the benefit-risk at the time this confirmatory trial has read out, and this takes into account any changes in the treatment landscape or any new available therapies. We also consider if there are any other potential safety advantages

over other available therapies.

Again, given the overarching goals of this approval pathway, the key consideration in whether withdrawal is warranted is still this balance of early access to these drugs for patients with cancer against uncertainty that clinical benefit may in fact not be verified.

To facilitate timely completion of these confirmatory trials at the time of accelerated approval, timelines for both a confirmatory trial completion, as well as the final report submission which contains these trial results and the study data, are agreed upon by both the applicant and FDA. In practice, this means that specific milestone dates for the confirmatory trial completion and submission of results to FDA are included in the accelerated approval granted letter.

FDA has the authority to ensure that these confirmatory trials are completed in a timely manner. In fact, accelerated approval legislation allows that such an approval may be withdrawn if

these post-approval studies or confirmatory trials are not completed with due diligence. In oncology, we interpret this to mean that the confirmatory trial should be completed in the shortest time period that is reasonable, taking into account the disease and any unmet medical need. Again, withdrawal here is not an automatic decision and is considered in the context of current available therapies to balance patient access against continued uncertainty, and you'll see an example of this patient-centric approach later today with the PTCL products up for discussion, where FDA is not asking the committee to decide if these products should be removed from the market.

The oncology experience is critical to understanding these delays after accelerated approval. To date, the majority, or 60 percent, of accelerated approvals have been granted in oncology, which we can see here on the graph in blue compared to non-oncology accelerated approvals in orange. This proportion has only been increasing in recent years with oncology

indications accounting for a greater and greater percentage of FDA's accelerated approvals over time.

So far, 187 accelerated approvals have been granted in oncology for unique drug indication pairings, and of these, 65 are still ongoing, and we are awaiting the readout of confirmatory trials or are currently reviewing these trial results in-house. For 96, the confirmatory trials have already read out favorably and have verified clinical benefit. In these cases, traditional approval has been granted a median of 3.1 years after the accelerated approval, so this suggests that these drugs are being made available to patients with cancer several years earlier than had they been developed through traditional pathways alone.

Finally, for 26, the confirmatory trial was either not completed or did not verify clinical benefit, and the indication was withdrawn. The majority of these have been labeling changes to remove the indication; however, in only 9 cases was

the drug removed completely from the market. Overall, this withdrawal of an indication has occurred a median of 4.1 years after accelerated approval, and it's really this lag time that we plan to explore today since this represents the amount of time when a drug that likely does not confer a clinical benefit remains on the market.

So this leads us to our first major topic, this risk of delayed confirmatory trials. As we've previously described, this period from the time of accelerated approval to the time the confirmatory trial is completed and a subsequent action is taken by FDA, which is highlighted with the red arrow here, is a period of vulnerability during which there's potential for patients to be exposed to a drug product that may not confer a clinical benefit.

This suggests that the risk of accelerated approval is not simply the risk that clinical benefit is not verified and drug is withdrawn; rather, the risk of accelerated approval is a function of this risk that the benefit is not

eventually verified, multiplied by the time that the drug stays on the market and is made available to patients, and we can reduce this overall risk by reducing this time to verification of benefit.

In general in oncology, this time to verification of benefit and subsequent action by FDA, meaning either conversion to traditional approval or withdrawal, has improved over the decades, and we need to be careful about how we analyze trends in this time to verification or refutation of benefit because more recent accelerated approvals are limited in the amount of time they may be delayed.

To account for this and capture the effect of ongoing accelerated approvals, we used Kaplan-Meier analyses to quantify the time to traditional approval or withdrawal for accelerated approval if granted in the 1990s, the 2020s [2000s - sic], the 2010s, and the 2020s. As you can see, the the median times for traditional approval or withdrawal for an accelerated approval granted in the 1990s was 5.6 years. This median

has improved to 4.7 years in the 2000s and 3.7 years in the 20-teens. The median has not yet been reached for accelerated approvals granted in the 2020s since many of these approvals are still ongoing.

Finally, when we look at the current state of ongoing oncology accelerated approvals, again, these are approvals where we are still awaiting the results of the confirmatory trial. Eighty-five percent of them have been granted within the past five years; so, in general, most of these are quite recent and not overly delayed. There are some significant outliers, however, and later today you'll hear about the two oldest ongoing oncology accelerated approvals, pralatrexate and belinostat, seen in red in the graph on the right, which have been ongoing for over 14 and 9 years, respectively.

Now that we've discussed the risks of delayed confirmatory trials, we can focus our attention on some of the causes of these delays. Whether the confirmatory trial is underway at the time of accelerated approval appears to have a

considerable effect on the time to verification of benefit. We reported on this last year, in the New England Journal, that this time to subsequent action -- meaning, again, either traditional approval was granted or the indication was withdrawn -- is reduced if the confirmatory trial is underway at the time of accelerated approval. Looking at today's numbers, this time to subsequent action has been a median of 3.1 years if the confirmatory trial was underway and a median of 7.3 years if the confirmatory trial was not underway.

Other factors can also impact the overall feasibility of the confirmatory trial. These include the effect of the accelerated approval itself, since simply having the drug available on the market, particularly if it's being studied in the same line of therapy, may limit enrollment to the confirmatory trial.

Additionally, changes in the treatment landscape and specifically the approval of new available therapies for the disease can also affect

trial enrollment. And finally, a change in the incidence of the disease could affect enrollment. We saw this with delays in the confirmatory trial for Doxil for Kaposi's sarcoma, which was slow to enroll after the advent and uptake of highly active antiretroviral therapy in the late 1990s.

In addition to the previously mentioned causes of delays, you'll hear about additional reasons for confirmatory trial delays later today in the focused discussion regarding the two products for peripheral T-cell lymphoma, and you will hear later today that in addition to the confirmatory trials not being underway at the time of these accelerated approvals, in these cases, the combination dose was not established and is currently being studied in a confirmatory trial. Compounding these issues, there have also been administrative delays.

So given these risks and a better understanding of the underlying causes of delayed confirmatory trials, we'll turn our attention to strategies that sponsors can take to help minimize

this risk or the time to verification of clinical benefit. Sponsors who are considering accelerated approval should have a comprehensive development plan that not only includes the trials to support the initial accelerated approval but also prespecifies a path to verification of clinical benefit, more specifically, the confirmatory trials.

Sponsors may want to consider multiple paths to verification of benefit, particularly if the primary confirmatory trial is in a different line of therapy than the original approval. In planning for an accelerated approval, sponsors should also consider the timing of when they initiate the confirmatory trial and should determine rational timelines for completion of these trials.

Ideally, confirmatory trials will be well underway at the time of accelerated approval. Having the trial be fully enrolled or near full enrollment helps to obviate some of the risks we discussed earlier. This includes the effect of the accelerated approval itself on trial enrollment;

the effects of changes in the treatment landscape, and specifically new available therapies; and any potential administrative delays related to trial initiation or opening of study sites.

The timelines for trial completion should also be realistic and data-driven. This should be based on the projected accrual that's informed by the disease incidence and the disease natural history and should also incorporate the potential effect of the accelerated approval on accrual. Again, the availability of the drug on the market in the U.S., and in some cases globally, has the potential to affect confirmatory trial enrollment.

Other regulatory health authorities around the world have built on the model of accelerated approval and have developed analogous expedited approval programs of their own. In some countries or regions, these programs incorporate alternative strategies to mitigate this risk of delayed verification of benefit. This includes the European Union; the United Kingdom; Australia; and Switzerland, where the expedited approval must be

renewed.

In some of these cases, there's even a maximum time limit on the expedited approval. This time limit is only two years in Switzerland but may be extended in exceptional cases, and in Australia, this time limit is a maximum of six years. Although this strategy is employed elsewhere, this may not be an effective solution in the U.S. because it does not allow flexibility for rare diseases or those with long natural histories.

FDA has new regulatory authority to minimize delays, and the impetus for this was largely based on our three decades of experience with accelerated approval and a better understanding of the implications of delayed confirmatory trials. In December of last year, Congress passed the Food and Drug Omnibus Reform Act, or FDORA, which allows FDA to require confirmatory trials be underway prior to approval. It also requires that progress reports on the confirmatory trials be submitted by sponsors twice a year, adding to the transparency of the program and most importantly allowing us to

identify and address delays earlier on. Finally, the legislation includes a streamlined withdrawal process, which should further limit the exposure of U.S. patients to drugs that are found to not verify clinical benefit.

Finally, the FDA's Oncology Center of Excellence is also addressing delayed confirmatory trials through the establishment of Project Confirm. This is an initiative to increase transparency around the use of accelerated approval in oncology, and thereby increase accountability. Project staff maintain a public searchable database of oncology accelerated approvals that's updated in real time. We also provide public education on the program and support data analyses and opportunities such as today's meeting to improve program outcomes. You can learn more about the project at the website listed below.

So as we conclude, it's important to remember that accelerated approval allows patients with cancer early access to potentially life-saving drugs. Classically, we've measured the success of

this program as the percentage of drugs that go on to verify clinical benefit. In reality, it's expected that some proportion of accelerated approvals will not have clinical benefit verified, and this is why the program exists.

Alternatively, we can consider the measure of success with this program to be how we minimize risk by minimizing delays in confirmatory trials and verification of benefit. We've talked about some of the causes of these delays; however, fortunately, as we gain greater experience with this program, this time to verification of benefit continues to improve.

Finally, we can continue to further improve and minimize delays in confirmatory trial completion moving forward. This ideal can be achieved by having sponsors approach accelerated approval with a comprehensive development plan and by having the confirmatory trials be well underway, or at least underway at the time of accelerated approval, and by identifying rational and data-driven timelines for completion of these

confirmatory trials. This approach is supported by new regulatory authority granted in the FDORA legislation, and finally by increasing transparency and accountability as we're doing today. Thank you, and we look forward to your questions and discussion later today.

Clarifying Questions

DR. CHEN: Thank you, Dr. Mehta.

We will now take clarifying questions for Dr. Mehta. Please use the raise-hand icon to indicate that you have a question and please remember to lower your hand by clicking the raise-hand icon again after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for my questions," so that we can move on to

the next panel member.

We will begin to take questions now.

Dr. Thanarajasingam, please.

DR. THANARAJASINGAM: Hi. This is Gita Thanarajasingam from the Mayo Clinic. Thanks for that presentation. I think there's no question about the need for therapies in relapsed refractory PTCL, and I think that for the FDA to defend public safety, there's also no question about the need for timely confirmatory studies to verify benefit and also lack of toxicity that can affect survival outcomes, as we've seen in other situations. But I really think that what's less clear is what constitutes a feasible and appropriate confirmatory trial.

While I recognize the barriers to completing the confirmatory study in the same population for which the accelerated approval was obtained, as you very well outlined, at the same time, as a clinician, I struggle with affirming benefit and understanding toxicity in a relapsed/refractory population when we're testing the drug in

combination with cytotoxic chemotherapies in front- or first-line treated patients. The biology and the disease outcomes are different, and treatment that fails to augment efficacy of currently front-line standard treatments may still be a really valuable one at relapse, plus the toxicities and tolerability of a single-agent therapy in the relapsed/refractory setting may be less than in combination with front-line chemo, so the math is entirely changed.

I recognize the conundrums and the challenges you pointed out, but I think there are strategies to overcome this. I'll ask about those in later questions to the sponsor and the FDA. But for now, Dr. Mehta, do you think the FDA thinks there are opportunities for confirmatory studies in the same population with the accelerated approval, and would a confirmatory study in the original population, that may be smaller in combination with the front-line trial, be something that is reasonable or feasible if a sponsor can do it? Thank you.

DR. MEHTA: Thank you. Because this question is perhaps product specific, I'll turn this over to Dr. Yvette Kasamon to respond first; and actually, maybe Dr. Pazdur first.

DR. PAZDUR: Let me address that issue because the idea of doing confirmatory studies in a slightly different indication has been present for the past 20-plus years in the FDA's oncology perspective on this, and we've had important discussions publicly about this for many, many years.

We believe that letting sponsors do a confirmatory study or having these confirmatory studies in an earlier disease setting actually is a benefit to the disease itself, and more importantly to patients because it moves therapies up much quicker to an earlier line of therapy, where more patients will benefit and also the efficacy will be examined and realized much greater, so to speak. One would also hope that if the studies are effective in an earlier line of disease, the drug would be used in the earlier line of disease and

render, really, the refractory indication almost irrelevant because people are using it in a much earlier line of disease, and I think that is an important point.

One of the other issues is, obviously, if one is approving a drug and saying that it is safe and effective in a particular indication, it is going to be almost impossible to accrue patients to a trial to demonstrate it's safe and effective, so that would terminate all U.S., basically, accrual to that trial.

But here again, I think the overwhelming approach has been let's try to escalate drug development and move the ball forward more rapidly, rather than looking at only the most refractory disease population. And again, most of the accelerated approvals have aimed their registration strategy at very refractory patients because they're looking at single-arm trials.

We do have, in fact, Project FrontRunner ongoing, and we're looking for participants from industry really to move the accelerated approval

program away from just the most refractory patients to, really, earlier disease settings where the efficacy could be much better recognized, as well as the benefit to the patients, especially if we're talking about therapies that have breakthrough designation. But I'll turn it over to the disease-specific people to comment.

DR. KASAMON: Hi. Thank you. This is Yvette Kasamon. Thank you for that question. As Dr. Pazdur mentioned, it's very common in oncology for the confirmatory trial to be conducted in a different disease setting. You've heard that the accelerated approval itself may affect enrollment to a confirmatory trial that's conducted in the same setting or the same population.

So, as was just noted, our general approach is to base the accelerated approval on a single-arm trial that's conducted in a more refractory setting and conduct the confirmatory randomized trial, or trials, in an earlier disease setting. This may allow extrapolation from one disease setting to another, while, as Dr. Pazdur mentioned, offering

patients with relapsed or refractory disease earlier access to new and potentially promising therapies. This confirmatory trial may evaluate monotherapy or combination therapy.

So we always evaluate the applicability of a proposed trial and the results within each disease setting. And as you've heard, there is a degree of uncertainty with accelerated approval endpoints, so we put the confirmatory trial results together in the context of the totality of the data, including the data from the accelerated approval. Thank you.

DR. CHEN: Thank you, Dr. Pazdur and Dr. Kasamon.

We'll move to Dr. Cheng for his question.

DR. CHENG: Good morning. I'm Jon Cheng, industry rep. Thank you to the FDA for raising this important topic. I think we all share the goals of trying to provide early access to life-saving drugs while balanced by minimizing delays, particularly in trials that do not confirm.

My question, I think initially to Dr. Mehta, is, can you comment on the confirmatory trials?

There are times where a confirmatory trial is not positive, but that doesn't mean that drug does not have benefit and requires a second confirmatory or a subsequent confirmatory trial. So can the FDA comment to not a confirmatory trial that confirms benefit, but a confirmatory program that allows you a number of shots to be able to confirm benefit? Because oftentimes we learn from the confirmatory trials that do not reach clinical or statistical significance to design a subsequent trial, but that will then result in subsequent delays to a potentially asset to be confirmed.

So can you comment on a single trial versus multiple trial options, and then subsequent trials, to allow an accelerated approval to then be delayed but still be able to allow it to be confirmed based on the knowledge gained from a potentially negative confirmatory trial?

DR. MEHTA: Well, I think you've touched on a lot of important topics that we think about a lot regarding this confirmatory trial. You mentioned the term "confirmatory program." Sponsors can take

an approach where there are multiple approaches ongoing concurrently to address verification of benefit. Sometimes if accelerated approval is granted in a later line of therapy, and then verification of benefit is being tested in an earlier line of therapy, it may be possible that against that front-line therapy, the drug granted accelerated approval may not win. So that doesn't necessarily mean that this is a failed drug or that this drug still doesn't work in that later line of therapy or is safe and effective.

One approach would be having multiple ongoing trials that address both the earlier lines and the later lines at the same time. But I think you mentioned if the confirmatory trial fails, then how do we look at things. At that time -- and I mentioned this a little bit in my talk -- we, again, reassess the situation. We're looking at the disease landscape and we're looking at the outcomes of that confirmatory trial. If that confirmatory trial shows a clear survival detriment or that this drug is unsafe, then I think maybe the

results are very unequivocal. But if the results are equivocal, the confirmatory trial does not reach the primary endpoint but at the same time there is information that suggests that maybe this drug is still safe and effective, there may be a role for studying it in additional confirmatory trials that could be done at that point. In those cases, we have released and reissued the accelerated approval PMRs and allowed companies to pursue another confirmatory trial.

I think what's important here is, again, we're reassessing the drug at the time that confirmatory trial reads out. So if there are new available therapies that show benefit in that space and that trial does fail, then the drug may be withdrawn from the market.

DR. PAZDUR: One of the points I want to make is a failed trial does not mean a failed drug, and I think that's important for the committee to understand. We saw this quite dramatically at an ODAC presentation when we went over the multiple accelerated approvals for the PD-1 drugs and, here

again, we were dealing with a class of drugs that many people considered these drugs very, very, very similar. Some of the trials failed, some of them succeeded, but many of them were very similar, the trials.

There are areas of clinical trial methodology that may render the demonstration of clinical benefit difficult, and we saw that because we had positive trials and negative trials for the same class of the disease in the same disease setting, and those could be due, for example, to underpowering of the trial; selection of the wrong population, PD 1 positive versus the ITT population; and hierarchical testing of drugs, whether the trial was an add-on design versus a head-to-head comparison. So that was quite illustrative of the concept that a failed trial does not mean a failed drug.

As Gautam pointed out, we do assess at that point, then, what is the current landscape. Is there a need for this accelerated approval? Because here again, if we're reissuing a letter

asking for another confirmatory study, this period of vulnerability, so to speak, is going to be now 3-, 4-plus years while somebody writes a trial, gets it through the system, so to speak, and then accrues patients to it.

DR. CHENG: Thank you.

DR. CHEN: Thank you for that discussion.

Dr. Advani, your question, please?

DR. ADVANI: Thank you. This is Dr. Advani.

Dr. [indiscernible], I struggle to understand that PTCL, in general, is probably one of the most heterogeneous entities, not only clinically, but even at a molecular level. Are there other examples in oncology where you have such a big heterogeneous population where one agent is being studied and how long that has taken?

The second question is, do you ever consider outcomes based on real-world data for these very, very rare diseases, which when you break it up into different subsets to see, overall, if there's an improvement in survival, which might help explain or help prolong the timelines? Thank you.

DR. MEHTA: Maybe I can address the first question, and then I'll turn it over to Dr. Kasamon for the second question. I think we've gone through this experience with different cancer types in the past, and the cancer treatment landscape has evolved quite a bit in the past couple of decades. For example, with lung cancer, non-small cell lung cancer used to be what we now know to be a very heterogeneous population, and drugs were approved in those settings, but we have more information now. We have history with understanding these heterogeneous populations and studying them, but maybe I should hand it over to --

DR. PAZDUR: Let me make this comment. I think you're pointing out a problem that's occurring throughout oncology, or not a problem, but a challenge. All of the diseases that we have and we're recognizing are heterogeneous diseases. Gautam pointed out lung cancer, and the same thing could be said about breast cancer, obviously.

So what we've done is as these subsets become identified as "distinct diseases," quote, if

they are small, then we will be realistic and say you can't do a randomized study here. You can't look at overall survival in a patient population that is quite small. So we have granted accelerated approval on the basis of response rates, and frequently the confirmatory evidence, not necessarily trial, is basically adding more patients in a single-arm trial to gain clarity on the response rate, as well as the safety of the drug.

We have to be realistic that in every situation, one cannot do a large randomized trial, and those could be because of the small numbers of patients; very long natural histories of the disease; the fact that there might be equipoise that does not allow randomization, so there are many reasons a randomized study cannot be done. So we have -- especially in lung cancer, I think, as a great example with the number of mutations -- granted accelerated approval on a response rate that is quite persuasive, and high, and of long duration, and then sought confirmatory

evidence for that conversion based on enrolling more patients and basing the actual full approval on response rate alone. We just have to be realistic about the situation here.

As far as real-world data, that's something that we're always looking at it. It's very difficult, though, to look at a time-to-event endpoint such as overall survival and compare it to a population, a small population, and then try to say that these populations are identical. Here again, real-world data has many areas that we're exploring at the FDA; however, I think we would not at this time take a look at overall survival of an arm on real-world data. It may provide confirmatory evidence based on that topic, but as far as the subsequent conversion, we'd probably prefer to see more response rates, and then look at that real-world data.

DR. CHEN: Thank you.

We are running a little bit behind schedule, so please focus your questions and discussion, if possible, and I would like to remind everyone to

state their name before each time they speak.

Dr. Nieva, you're next.

DR. NIEVA: Thank you. This is George Nieva from USC. My question is for Dr. Mehta. When we think about the speed at which trials are conducted, often times that seems proportional to the input resources and capitalization that a company has available to spend on the conduct of the trial. This of course then translates to higher drug costs and potentially healthcare disparities. I'm wondering if the FDA has performed any type of economic analyses or impact on healthcare disparities regarding the speed and input resources requested in terms of the conduct of these confirmatory trials. Thank you. That concludes my question.

DR. MEHTA: Thank you, Dr. Nieva. This is Gautam Mehta, FDA. Today, we haven't performed any analyses, or economic analyses, on the speed or factors that have led to the speed of getting these confirmatory trials done. It's certainly an important point. I think that also circles back to

the point that pursuing a development program for accelerated approval is a commitment not only to achieve that initial accelerated approval or have a study that supports that, but also you'll have studies that will verify a clinical benefit or have adequate resources committed to these confirmatory trials. So it is a little bit of a commitment. I think we haven't looked at small companies versus large or the amount of resources, but it's an important consideration.

DR. PAZDUR: The only point I have to make is, really, the whole purpose of the accelerated approval program is patient-centric, and I've made this comment multiple times. It was never meant as an incentive program for the pharmaceutical industry. It's really patient-centric to get a really innovative drug out earlier to a patient population with the commitment that further studies be done and further elucidation of the drug's benefits be brought out.

I think that's an important point, that this is not an incentive program for the pharmaceutical

company, but came from the AIDS arena -- AIDS era, rather, I should say -- and a need for innovative therapies, and I think that this has been very widely used in oncology drug development.

DR. NIEVA: Thank you.

DR. CHEN: Thank you.

Dr. Choueiri, this will, unfortunately, be the last question for this section, as we have to move on after this.

DR. CHOUEIRI: Thank you. Toni Choueiri, Dana-Farber Cancer Institute, Boston. First, congratulations, Dr. Mehta, on an impressive and very clear presentation about the program. My question is, despite the best intention from the sponsor, the FDA, the patient, and everyone, it is very possible that the follow-up studies may not happen for multiple reasons. The most important will be, in my fair opinion, accrual.

I suggest to this committee to launch the confirmatory studies around the time of approval and to have a serious follow-up every 6 months perhaps about the accrual. I think the accrual

could happen also outside the United States because at this time, if the accrual for whatever reason, things are not on, the patients are not being accrued well, we could look at never having confirmatory studies, and that is not good for patients and that is not good for the field. Thank you.

DR. MEHTA: Thank you, Dr. Choueiri. This is Dr. Mehta again. I think you raised important points regarding accrual that are actually addressed, fortunately, in the new FDORA legislation, that grants FDA regulatory authority to now require that studies be underway at the time we grant accelerated approval, so that's one part of it.

You also mentioned following up on studies every 6 months. Sponsors are now required to submit to us progress reports on their studies every 6 months, in fact. So I think this will help both the sponsors and us keep better tabs on these confirmatory trials, and we can see if there are issues with accrual and spot them earlier as

opposed to 3 or 4 years down the line when we're still wondering why this confirmatory trial hasn't read out. So definitely, we would like to move these issues up earlier so we're not dealing with them with significant delays.

I think one additional point I'd like to add is, ideally, we'd like trials to be actually well underway, so largely enrolled at the time accelerated approval is granted, these confirmatory trials that is. That helps really get around some of these issues that I brought up in terms of difficulty with accrual and issues when the accelerated approval has been granted, and now the drug is on the market and it's hard to enroll patients to these confirmatory trials, at least in the U.S. Thank you.

DR. PAZDUR: One of the advantages of having the trial underway is not only the timeliness, but also the feasibility, i.e., can the trial be done? I think this is an issue that we have seen throughout the years, as many times sponsors propose a trial as we're writing the approval

letter, so to speak, and the trial simply can't be done. It's not feasible if clinicians don't want to do it. There are multiple other issues here that come into play, but the feasibility issue is also one that has to play into consideration of why we want these trials to be underway; can the trial be done?

DR. CHOUEIRI: One small follow-up question -- it's very short -- is, what is the threshold for you, Dr. Pazdur or Dr. Mehta, to say that we tried everything possible, we gave the sponsor every chance, and this is not happening for multiple reasons; and that way, we are taking out the FDA approval? Is that an option?

DR. PAZDUR: Well, we always take a look at that. We have to examine the landscape at that time. Obviously, these drugs are approved usually on response rates in a disease where there is no effective therapy. These are not placebos. There is biological activity here, so that's different from perhaps other therapeutic areas, so there is some biological activity. Then we would have to

take a look at what is the therapeutic landscape at that time. Is it in the public's best interest to have this not dangling accelerated approval but prolonged accelerated approval here? So that is a case-by-case basis that we would do.

And remember, these trials should be done with due diligence and, here again, when you're going out years and years and years, people could make a cogent argument that they have not done these trials with due diligence.

DR. MEHTA: And maybe one quick follow-up to that is if we do see that a confirmatory trial is stalled or a program is stalled, we do encourage bilateral discussions with FDA so we can try to work around these problems or see if there are other paths forward. So I think it's not necessarily a black and white decision at that point. We still want to have more conversations with the companies and we want to have these conversations before they get to the stalls. But again, we're encouraging this discussion upfront.

DR. CHEN: Thank you.

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

FDA Introductory Comments - Nicholas Richardson

DR. RICHARDSON: Good morning. I'm Nicholas Richardson, a hematologist/oncologist and the deputy director of the Division of Hematologic Malignancies II, which oversees the development of products for patients with lymphoma and multiple myeloma. To the chair, the committee, the sponsor, and everyone joining us today, we look forward to a productive discussion on two products with accelerated approval for adult patients with peripheral T-cell lymphoma or PTCL.

Today, we are seeking the committee's input on the prolonged accelerated approvals of pralatrexate and belinostat and the delayed verification of clinical benefit. As shown here, pralatrexate, a dihydrofolate reductase inhibitor, was granted accelerated approval in September of 2009, and belinostat, a histone deacetylase inhibitor, or HDAC inhibitor, was granted accelerated approval in July 2014. Both agents

were approved for the same indication and both approvals were based on a single-arm trial with a primary endpoint of response rate supported by durability.

Today's ODAC is different in nature, as we are here to discuss two prolonged accelerated approvals with delayed verification of benefit. There will be no voting question for our meeting today; thus, the discussion that we have here today is of utmost importance. We desire to have an inspection of the root causes that have led to the current situation with these two products, which are outliers for accelerated approvals. The discussion items are shown here and focus on the sponsor's current plan to verify clinical benefit and how insights from this experience can be leveraged for these products and other products with accelerated approval.

Importantly, we are not here today to discuss if these products should be withdrawn from the market. Because PTCL is a rare disease and patients that are relapsed or refractory have

limited treatments available, continued access to these therapies remains crucial.

With the discussion topics in mind, I'd like to review the regulatory approval pathways in the U.S. Traditional or regular approval is based on a demonstration of clinical benefit, which is generally a measure of how a patient feels, functions, or survives. This can also be accomplished by demonstrating an effect on an established surrogate.

Accelerated approval is intended for products that are designed to treat patients with a serious or life-threatening illness. The product must provide an advantage, taking into account the condition and the available treatments, and the approval is based on an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint other than survival or irreversible morbidity, what is referred to as an intermediate clinical endpoint. Because of the endpoints used to support accelerated approval, post-approval trials may be

required to verify clinical benefit.

As noted in Dr. Mehta's presentation, accelerated approval is a convergence of the effect on either an early clinical endpoint or a surrogate endpoint that is reasonably likely to predict clinical benefit and whether the effect is balanced against some uncertainty that the drug may not provide direct clinical benefit. The way we prove or verify that clinical benefit is through confirmatory trials. To limit the uncertainty regarding clinical benefit or the period of vulnerability, confirmatory trials are to be conducted with due diligence.

Because a single-arm design and a response-based endpoint were used to support the initial approval of both pralatrexate and belinostat, a postmarketing requirement was issued for each agent to verify the clinical benefit. The current accelerated approval PMR for pralatrexate and belinostat is shown on the slide. The sponsor has chosen to pursue a randomized trial evaluating three arms: pralatrexate in combination with

chemotherapy, belinostat in combination with chemotherapy, versus a control arm of chemotherapy alone.

Prior to the initiation of this trial, the sponsor was required through postmarketing requirements to identify an optimal and safe dose of each agent in combination with chemotherapy. You will hear more about the dosing considerations and the timeline for these products in the FDA presentation. The important point we are here to discuss today is that we do not have evidence to verify the clinical benefit of pralatrexate and belinostat for patients with PTCL despite initial accelerated approvals 14 years ago and 9 years ago, respectively.

In oncology, early endpoints such as objective response rate and progression-free survival have been extensively used to facilitate early access to much needed therapies for patients with cancer; however, recent oncology trials have highlighted a lack of correlation between these early efficacy endpoints and overall survival,

reinforcing the need for verification of clinical benefit for products granted accelerated approval based on an early intermediate clinical endpoint.

This table highlights a selection of some of the recent trials where a lack of correlation between [indiscernible] endpoints and overall survival has occurred. As seen in the first four rows of this table, in randomized-controlled trials in patients with chronic lymphocytic leukemia, indolent non-Hodgkin lymphoma, and multiple myeloma, we have seen a statistically significant advantage in progression-free survival supported by an improvement in response rate for the investigational arm but the overall survival results showed a potential detriment.

Conversely, in several immunotherapy trials like CHECKMATE-057 in patients with advanced, previously treated non-small cell lung cancer, a significant improvement in overall survival was demonstrated with no improvement in progression-free survival. The lack of correlation emphasizes that the relationships between these

early endpoints and overall survival have not been formally established, and this relationship may vary based on multiple factors such as the disease setting; the drug or drug class and the associated toxicity profile; the effect size on the endpoint; and available therapies. For randomized trials in patients with PTCL, PFS is commonly used as the primary endpoint. In randomized trials with a primary endpoint of PFS, overall survival remains a critical endpoint and is always evaluated by FDA and included in the evaluation of benefit and risk.

For today's discussion, it is really important to consider the disease context, available treatments, and the need for new therapeutic options for patients with PTCL. This figure shows the FDA approvals over the last 14 years in PTCL. From 2009 to 2014, four products were granted accelerated approval, all based on single-arm trials with a response-based endpoint that were supported by durability. For brentuximab vedotin, a CD30-directed antibody drug conjugate, the approval only applies to a subset of patients

with PTCL, namely those with CD30 expression; yet, brentuximab vedotin was granted traditional approval in 2018 after successful completion of a randomized trial that verified clinical benefit.

Alternatively, for romidepsin, an HDAC inhibitor, a phase 3 confirmatory trial was conducted in patients with previously untreated PTCL, which failed its primary endpoint of PFS and did not verify clinical benefit. The PTCL indication for romidepsin was voluntarily withdrawn by the company in May of 2022. The regulatory experiences with brentuximab vedotin and romidepsin in PTCL are important for today's discussion, and you'll hear more about them later in the FDA presentation.

As you can see, there have been a limited number of approvals in patients with PTCL, and there remains a need for effective therapies for these patients. Because of the disease setting and the current PTCL treatment landscape, continued access to these treatment options remains important. Again, the primary aim for today's

meeting is on the sponsor's current plan to verify clinical benefit for pralatrexate and belinostat, and how insights from this experience can be leveraged for these products and other products with accelerated approval.

As you'll hear today, there are several reasons the sponsor has indicated that has led to the prolonged accelerated approvals of pralatrexate and belinostat and the delayed verification of clinical benefit. These include the transfer of ownership of the products, leading to logistical delays; concerns regarding dosing, toxicity, and tolerability; and the need for further evaluation of a safe and adequate dose for each product in combination with chemotherapy. These have culminated in delayed initiation of the currently proposed trial to verify the clinical benefit for both drugs. With the trial just starting last month, finally, the currently proposed timeline includes an estimated projection of the results being available in 2030.

With that context in mind, we are asking the

committee to discuss the following topics. Number one, discuss the delays in post-approval confirmatory trials for pralatrexate and belinostat and whether the current plan to verify the clinical benefit of these products in patients with PTCL is reasonable considering the sponsor's proposed timeline. Number two, discuss strategies to promote timely completion of the confirmatory trial for pralatrexate and belinostat, and insights from this experience that may facilitate completion of confirmatory trials for future accelerated approvals.

Again, there is no voting question for today's ODAC and the value of today's meeting will come from the discussion, and we thank you for your thoughtful insight and input on these important topics. Thank you. This ends my presentation.

DR. CHEN: Thank you, Dr. Richardson.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee

meeting, FDA believes that it is important to understand the context of an individual's presentation.

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

Applicant Presentation - Ashish Anvekar

MR. ANVEKAR: Good morning, members of the

FDA and the advisory committee. I'm Ashish Anvekar, president of Acrotech Biopharma. Thank you for the opportunity to provide an update on the postmarketing requirement studies, or PMR studies as we will refer to them in the presentation. This update will focus on the confirmatory phase 3 PMR study status, wherein we will share the plan and execution details with regards to this trial.

To provide a context, Acrotech acquired these products in March of 2019 and recognize the delayed status of the studies, and we have made progress in completing the studies as per their planned designs. We recognize that as the current NDA owner, we are responsible for completing the PMRs. Completion of the confirmatory PMR is our main goal. I personally thank the patients who have and will participate in these trials, and the time and energy they have contributed is invaluable. Let me begin with some background on the products.

Pralatrexate and belinostat both have accelerated approval for the treatment of relapsed

refractory peripheral T-cell lymphoma. For simplicity, we will refer to the disease as PTCL throughout the presentation. Pralatrexate is a dihydrofolate reductase inhibitor and belinostat is a histone deacetylase inhibitor. Both drugs are designated by the National Comprehensive Cancer Network, or NCCN, as Category 2A preferred treatment regimens.

PTCL is a rare, aggressive, and heterogeneous disease affecting 10,000 to 15,000 patients in the U.S. These patients have limited treatment options available in the first-line and relapsed/refractory setting. Throughout the disease course, most patients will relapse and require additional lines of therapy, so there is a need for products with different mechanisms of action that can be used across multiple lines of treatment.

With that background, let me provide a status update on the main confirmatory PMR trial. The main confirmatory PMR still needs to be completed, and we acknowledge the need to complete

our accelerated approval obligation in a timely manner. The confirmatory trial has gone through design changes since the product approved. When pralatrexate was approved in 2009, two confirmatory PMR studies were agreed upon. Upon belinostat approval in 2014, these PMRs were released and were replaced with an alternate trial design, a single phase 3 study in the first-line PTCL with three arms, pralatrexate plus CHOP, belinostat plus CHOP, compared with CHOP alone.

A dose-finding study had to be completed first to support the dose for each drug to be used in the confirmatory phase 3 trial. These dose-finding studies were initiated in August of 2014. In October 2016, the belinostat plus CHOP study was completed; however, the pralatrexate plus CHOP study was still recruiting patients. When Acrotech acquired the products in March 2019, we focused on completing the enrollment. After enrollment and the required follow-up of one year as per protocol, we submitted the CSR by October 2021 for pralatrexate plus CHOP study. We

shortly thereafter submitted the final phase 3 protocol for approval in March of 2022 so that we could initiate the confirmatory part of the study.

An amendment to the trial design was requested to identify the optimal dose for each product in line with Project Optimus guidance. As a result, we modified the protocol to make it a two-part study. Part 1 would evaluate 2 dose levels each of the products prior to beginning the confirmatory portion of the study in Part 2. Along with a few other protocol changes, we reached alignment with the FDA on the protocol in January of 2023 and initiated the start-up activities for Part 1. We are happy to report that the first site for the phase 3 study was activated in October 2023.

There were other smaller PMR studies which were also required, and briefly the status is as follows. For pralatrexate, four out of these five PMR studies have been completed. The single remaining pharmacokinetic studies are targeted to be completed by December 2024 and a CSR submission

5 months thereafter. For belinostat, these seven PMR studies have been completed. The highlighted studies are the ones completed or underway by Acrotech after acquiring the product in 2019.

Turning now to the remainder of the agenda, first, Dr. Owen O'Connor will present background on the disease and the role of pralatrexate and belinostat, including the studies that supported their accelerated approvals and real-world evidence; then, Dr. Swaminathan Iyer will present the results from the phase 1 PMR study and the design of our phase 3 study. I will then come back to present more details of the execution of the confirmatory PMR trial. All outside experts have been compensated for their time and travel to today's meeting. Thank you. I'll now turn the lectern over to Dr. O'Connor.

Applicant Presentation - Owen O'Connor

DR. O'CONNOR: Thank you, Ashish, and good morning, everyone. My name is Owen O'Connor, and I am an American Cancer Society Research professor and director of the Translational Orphan Blood

Cancer Research Center at the University of Virginia Comprehensive Cancer Center. I've been involved in developing drugs and taking care of patients with peripheral T-cell lymphoma now for almost 25 years. Over that time, I've contributed to the development of essentially every drug approved for the disease and was a co-inventor of pralatrexate, along with Francis Sirotnak, when I was on faculty at Memorial Sloan Kettering Cancer Center.

I'd like to say we've made enormous progress over that time, but as I will discuss, progress has been slow for a host of reasons, and the field still struggles with how best to help patients with this challenging disease. It's been over a decade since I made the case for the accelerated approval of pralatrexate before your predecessors on this committee. I'm here today to discuss the continued medical need I see in patients with PTCL and the challenges that come with improving patient outcomes given the rarity and biological heterogeneity of the disease.

First, let me share some background on the disease. So why has progress been particularly slow in PTCL? First, they are rare. According to the latest SEER data from 2011, the peripheral T-cell lymphomas have an incidence of about 10,000 to 15,000 cases per year in the United States, of which even the most common subtype might have an incidence of only 2,000 to 3,000 cases per year. There are about 15,000 medical oncologists in the United States, so this means each oncologist could expect to see a case of PTCL about once a year, if spread out evenly.

Second, the PTCL are remarkably heterogeneous. The latest 2022 WHO classification now recognizes 36 distinct subtypes. Unlike B-cell lymphoma, which is comprised of many indolent subtypes, most forms of PTCL are considered highly aggressive diseases. In essence, the PTCL are 36 orphan diseases lumped under an orphan disease. These features all conspire to make the conduct of clinical trials, let alone randomized clinical trials, exceedingly difficult.

Importantly, front-line conventional chemotherapy programs are not highly effective and there is no unified standard of care. CHOP-based chemotherapy is often regarded as the standard of care. CHOP was developed in patients with aggressive B-cell malignancies, a radically different disease. In fact, the pivotal study published in the New England Journal of Medicine in 1994, which led to CHOP being designated the standard of care, does not even mention PTCL, nor is there any evidence that a single patient with PTCL was ever treated on that study.

CHOP is commonly designated the standard of care because it's the most commonly deployed chemotherapy regimen used by the preponderance of physicians who treat the disease. This doesn't make it the optimal treatment available. Furthermore, CHOEP, which integrates etoposide into the CHOP backbone [indiscernible], represents another regimen widely regarded as a standard of care.

CHOEP obtained this status based on a

retrospective study, where they compared and contrasted dozens of different chemotherapy regimens, some containing etoposide, some not, seeking to determine whether the simple addition of etoposide across a remarkably heterogeneous group of chemotherapy regimens made a difference. Despite the lack of any statistically significant difference in the retrospective analysis, CHOEP earned the status and as an alternative standard of care despite a significant increase in toxicity.

The poor outcomes seen with conventional chemotherapy and the lack of any consensus on a standard of care have led the NCCN to recommend a clinical trial as the preferred treatment of patients in the front line and beyond. Other than the 10 percent of patients with PTCL who have systemic anaplastic large cell lymphoma, who benefit from BV-CHP, there has been no therapy developed which has improved outcomes for all the other subtypes of the disease.

The remaining 30-plus subtypes, accounting for about 90 percent of all cases, are typically

lumped and treated with standard CHOP- or CHOEP-based chemotherapy. This rarity, heterogeneity, and aggressiveness of the PTCL have made the development of standard of care exceedingly difficult, so to then come as no surprise, the field has produced little to no evidence that we've changed the natural history of PTCL in over 30 years.

As I'll discuss in detail shortly, there are several lines of data that would suggest that newer drugs, pralatrexate and the HDAC inhibitors, for example, are producing clinical benefit for this population, benefit that consistently seems better than what we have come to expect with traditional chemotherapy.

While we have made remarkable progress in the treatment of B-cell malignancies, the data from this graph depicts the progress for diffuse large B-cell lymphoma. As shown in the top blue line, the addition of rituximab to CHOP has improved overall survival for patients with DLBCL compared to CHOP alone, as shown in the red line. The black

and orange curves show how poorly patients with PTCL and the related NK-cell lymphomas do in comparison. These data, in essence, underscore the relative ineffectiveness of CHOP in PTCL.

Across a variety of studies, irrespective of subtype, the PTCL are now recognized as having the worst outcome of any blood cancer. In general, the median overall survival is less than 2 years and 5-year overall survival, less than 30 percent. In a large retrospective international study, the International T-Cell Project, approximately two-thirds of patients suffered a relapse or had refractory disease in the first year. These patients would go on to receive additional therapy, assuming they are even candidates.

In the right-hand panel, you can see the overall survival as a function of the common subtypes. As you can see, the blue line represents the latest data for systemic anaplastic large-cell lymphoma as reported in the ECHELON-2 study, while the red line shows the overall survival for ALCL seen with CHOP prior to the introduction of

brentuximab. The remaining subtypes have not seen any improvement in their outcome over the past several decades. Finally, while patients deemed transplant eligible will more often than not get an autologous stem-cell transplant, it's entirely unclear if this is a beneficial approach, though some retrospective studies suggest there may be a modest clinical benefit.

The limits of traditional chemotherapy for relapsed or refractory PTCL are underscored in the next slide. In this interesting study by Mak and colleagues from the British Columbia Cancer Agency, the authors examined the prognosis of patients from the point of their first relapse; that is, how do patients do with the available therapies in the relapsed setting? As this study was reported in 2013 in Canada, prior to the widespread introduction of the drugs under discussion today, it reveals the outcomes seen with traditional chemotherapy.

The second progression-free survival, that is the PFS resulting from the first treatment given

in the relapsed or refractory setting, was only 3 to 4 months with a second overall survival of only 6 to 7 months. These data largely reflect the ineffectiveness of traditional chemotherapy in the relapsed or refractory state, a finding that is remarkably concordant with the findings of the International T-Cell Lymphoma Project and a large case-match control study published by my team. For sure, patients aren't doing better with each subsequent line of therapy, so in theory, this is as good as any relapsed or refractory patient can do.

For me, what these data tell us is that subsequent lines of treatment, treatments that are essentially predicated on traditional chemotherapy in the relapsed or refractory setting, are not providing any meaningful benefit. Since the bulk of these data were collected prior to the significant use of the single agents approved for the disease in the U.S., in my opinion, it largely represents the limitations of our conventional chemotherapy approach.

So let's turn our attention to some general concepts around the treatment of patients in the front line. Regrettably, the front-line treatment of PTCL has remained largely unchanged for nearly three decades, save the ECHELON-2 experience. One important consideration here is that in the case of aggressive B-cell malignancies where rituximab markedly improved the outcome of virtually every patient when combined with CHOP, we have not discovered any R equivalent in PTCL despite the early excitement around brentuximab vedotin.

The notion of identifying an agent to improve upon the outcome of CHOP in PTCL is predicated, to some extent, on the improvement seen with R-CHOP in the B-cell malignancies. There has been no biological agent shown to be effective across the diversity of PTCL subtypes. Leveraging drugs with relative lineage selective activity in combination with CHOP has been and remains a reasonable ambition. With the exceptions of systemic ALCL, NCCN recommends a clinical trial as the preferred treatment.

In the relapsed and refractory setting, since 2009, the drugs under discussion today have become integral to the management of relapsed or refractory PTCL. While none of these drugs are perfect, they do give physicians and patients options. Pralatrexate was the first drug approved for this setting, followed by the histone deacetylase inhibitors romidepsin and belinostat. The PTCL, for unclear reasons, seemed to demonstrate a unique sensitivity to epigenetic-based treatments.

All three of the drugs shown in this table were approved based on single-arm, phase 2, monotherapy studies. The efficacy data for romidepsin are similar to the other drugs. In 2021, the romidepsin indication for relapsed or refractory PTCL was withdrawn by the sponsor after a phase 3 of romi-CHOP versus CHOP failed to demonstrate any benefit over standard of care in the front-line treatment of patients with the disease.

As I mentioned earlier, brentuximab vedotin

is only approved for patients with relapsed or refractory ALCL and does not have any significant value in treating the non-ALCL subtypes. It's also worth noting that allogeneic stem-cell transplants can be curative in this setting, though the major challenge is getting disease control to last long enough to allow patients to move on to the transplant. Also, unlike many other forms of lymphoma, no CAR-T has been demonstrated to be clinically useful in PTCL, though many are under development.

So here you can see that in contrast to the B-cell malignancies, the PTCL really lack reliable treatment options and have no demonstrable benefits from any immunotherapy, be it monoclonal antibody, antibody drug conjugate, or cell therapy, as we have experienced for the B-cell malignancies. It's important to recognize that pralatrexate and belinostat are distinctly different from the chemotherapies traditionally used to treat the disease. Each drug offers a different mechanism of action.

Quite interestingly for me, these drugs exhibit a remarkable T-cell selectivity and have not been shown to have meaningful activity in any other type of cancer. Pralatrexate is a folate antagonist that has very high affinity for the reduced folate carrier, which efficiently internalizes the drug. Pralatrexate exhibits a host of unique effects on T-cell lymphomas. The IC50 in T-cell models is at least a log-fold more potent than any other antifolate, and T-cell lymphomas are at least a log-fold more sensitive than any other cancer cell line, including B-cell lymphomas.

In contrast, belinostat is a potent HDAC inhibitor. For reasons not entirely clear, this group of diseases is well established to be sensitive to epigenetically targeted drugs. The HDAC inhibitors have the effect of shifting chromatin from a transcriptionally silent state to one that is transcriptionally active. This transcriptionally active confirmation is thought to mediate the many mechanisms ultimately leading to

cell death, and importantly, the mechanism of action of these drugs do not appear to be cross-resistant.

Next, I'd like to briefly share the preliminary data supporting the accelerated approval of these two drugs. The primary efficacy data supporting the accelerated approval for pralatrexate and belinostat come from the PROpel and BELIEF studies, respectively. The overall response rate, based on independent central review, was 29 percent for PROpel and 26 percent for the BELIEF study. The investigator-assessed response was 39 percent for PROpel and about 23 percent for BELIEF. The median duration of response was 10.1 months for pralatrexate and 13.6 months for belinostat. These durations of response in PTCL are substantially better than what we typically see with any chemotherapy in this setting.

The major question, and one that is hard to answer without randomized data, is are we providing any clinical benefit for patients receiving these drugs? While we don't have the volumes of patients

that would allow us to readily answer this question, it's not because the field isn't thinking about it, or trying. In fact, the field has diligently worked with datasets it has, creating multiple large international registries and extracting data from completed and ongoing trials, all in an effort to better understand how these drugs might be helping patients.

The first randomized study ever conducted in patients with PTCL, and the first and only recently one conducted in relapsed or refractory disease, was a study called the LuMIERE study. LuMIERE was a randomized, phase 3 I chaired, that compared alisertib to dealers' choice, which consisted of gemcitabine, pralatrexate, and romidepsin. While the study was negative, failing to establish alisertib was better than the dealers' choice arm, based on endpoints of overall response rate and PFS, it produced some interesting findings.

In the dealers' choice arm, 51 patients received pralatrexate, where the overall response rate was 43 percent, while 23 received gemcitabine,

where the overall response rate was 35 percent, while a smaller number, 18, received romidepsin, where that overall response rate was 61 percent. Progression-free survivals in the pralatrexate and romidepsin cohorts were also substantially better than that seen in the gemcitabine-treated patients.

This study failed because the dealers' choice arm outperformed pre-study expectations. Although a subset analysis, this is probably the best data from a perspective randomized study showing pralatrexate and romidepsin were at least equivalent to, if not better than, that observed for a commonly used conventional chemotherapy, namely gemcitabine.

In my second example of supporting data, I share with you the findings from three independent single-arm studies of pralatrexate across Asia. Each of these studies led to the full regulatory approval of pralatrexate in Japan, China, and Taiwan. The overall response rate in these studies were reported to be 45, 52, and 57 percent, with a safety profile similar to or better than that

reported in PROpel. The duration of response and progression-free survival in these experiences was also a bit better than we reported in the original PROpel study.

It is likely these results were better than what we saw in PROpel because these patients were less heavily treated, which I believe is an important determinant in a patient's likelihood of response. Taken together, and with all of the caveats noted earlier about the absence of prospective randomized clinical trials, these data affirm a very consistent message that pralatrexate and HDAC inhibitors are helping patients, and that these data have led to expanded approvals around the world with results that look to be even better than what was reported in the original pivotal study.

Finally, the safety analysis from the PROpel and BELIEF studies confirm an acceptable safety profile. This table summarizes the safety profiles from the pivotal studies. All the safety profiles for each drug are a bit different. Both drugs have

an acceptable safety profile in a heavily treated population of PTCL patients, and the most frequently reported adverse events for pralatrexate revolve around mucosal inflammation and thrombocytopenia that are consistent with the expected safety profile for the antifolate class.

In the pivotal BELIEF study, the most commonly reported grade 3-4 adverse events were hematologic, again, usually thrombocytopenia. You can see that these adverse event profiles compare favorably with that shown for brentuximab. In post-approval use, one case of toxic epidermal necrolysis was identified for patients who received pralatrexate, while no adverse reactions have been identified for belinostat.

In conclusion, pralatrexate and belinostat are now the only FDA-approved drugs for patients with relapsed or refractory PTCL. In the relapsed/refractory settings, brentuximab is essentially resigned to systemic ALCL, as it has been shown to be relatively ineffective in non-ALCL subtypes of PTCL.

There is no standard of care, nor consensus, for the treatment of PTCL patients in the front line or beyond. The ability to administer pralatrexate and belinostat safely for extended periods of time can provide meaningful disease control and likely contributes to the prolonged duration of response observed. The situation, in fact, is so dire that even NCCN recommends clinical trials as the preferred treatment in both the front-line and relapsed setting.

Many independent studies, like those from Asia, LuMIERE, and the case-match studies I alluded to earlier, are uniformly consistent in their findings and support the notion we need to deploy these active drugs earlier in the line of therapy and explore novel combinations, which are producing meaningful advances in the field, as our own work has shown. The failure to change the natural history of PTCL over the past 30 years mandates that we need to explore all reasonable options.

Thank you. I would now like to introduce my colleague, Dr. Iyer, who will speak about the PMR

dose-finding studies.

Dr. Iyer?

Applicant Presentation - Swaminathan Iyer

DR. IYER: Thank you, Dr. O'Connor.

Good morning, everybody. I'm Swaminathan Iyer, and I'm a professor in the Department of Lymphoma and Myeloma, Division of Cancer Medicine at the University of Texas, MD Anderson Cancer Center, and also lead the PTCL lymphoma program only because of an outstanding multidisciplinary team. I'm also the first author of the recently accepted manuscript for the phase 1 pralatrexate-plus-CHOP study. I'll also be sharing the belinostat-plus-CHOP phase 1 study and the phase 3 study that is now underway.

FOL 101 and BEL 104 were both phase 1, open-label, multicenter, two-part, dose-finding, dose-escalation studies. The objective was to establish the safety and efficacy of pralatrexate and belinostat, both in combination with CHOP. Both studies enrolled patients with newly diagnosed, untreated, histology-proven PTCL who are

eligible for CHOP chemotherapy.

The demographics for most patients in both studies included white males, although 20 to 25 percent of the patients in the FOL-CHOP arm had African American ancestry and 10 percent of the other study, with a median age of 62 to 63 years. Many patients had a subtype of PTCL NOS, including PTCL NOS more in the FOL-CHOP arm and AITL in the BEL-CHOP arm.

FOL 101 was conducted in two parts. In Part 1, patients were treated with pralatrexate in combination with CHOP for dose escalation on days 1 and 8 of each cycle in five sequential cohorts. No patients experienced dose limiting toxicity. Per protocol, because the MTD was not reached, the 30-milligram per meter squared dose was selected for the expansion cohort. In the expansion cohort, 33 patients were treated. Treatment was repeated every 21 days for up to 6 cycles, and the patients were followed for one year from the first dose.

Here we see the high overall response rate

for pralatrexate plus CHOP. Among the 31 patients available for efficacy in the expansion cohort, the objective response rate with the IWG criteria was 84 percent, with 65 percent complete responses and 19 percent partial responses. There was an acceptable safety profile for pralatrexate plus CHOP. In the expansion cohort, there was one death not related to the study drug. Furthermore, 36 percent had serious adverse events, a similar percentage as the other cohorts, and 21 percent of the patients had adverse events leading to discontinuation or dose reduction. Overall, this study concluded that pralatrexate plus CHOP had a high overall response rate and acceptable tolerability at 30 milligrams per meter squared dose.

Next, let's look at the belinostat study. The BEL 104 was also conducted in two parts. In Part A, patients in Cohort 3 were treated with 1000 milligrams per meter squared of belinostat per day on days 1 to 3 of each cycle with standard CHOP regimen. In the next cohort -- that's

Cohort 5 -- patients received 1000 milligrams per meter squared of belinostat per day for five consecutive days of every cycle with standard CHOP. No patients were treated in Cohorts 1, 2, and 4. As no dose limiting toxicities were observed in Cohort 5, 1000 milligrams per meter squared on days 1 to 5 with CHOP was declared the recommended regimen for the expansion cohort.

In total, 15 patients were treated with a recommended regimen. Patients were treated every 21 days with up to 6 cycles of therapy or until the toxicity or disease progression. The overall response rate for the study BEL 104 was high at 86 percent in both Cohort 3 and the Cohort 5 plus expansion. Most patients achieved a complete response, including 71 percent in Cohort 5 plus expansion.

Overall, the safety profile for belinostat plus CHOP was acceptable. All patients experienced at least one adverse event in both cohorts. Serious adverse events were reported in 38 and 47 percent of the patients. In Cohort 5 plus

expansion, no patient discontinued or had to have dose reduction and only 2 patients had a belinostat dose interruption. Based on the results of the study, this concluded that belinostat plus CHOP was promising and effective with an acceptable safety profile for newly diagnosed patients with PTCL.

Now let's turn to the phase 3 belinostat-plus-CHOP and pralatrexate-plus-COP study for the first-line PTCL, the final postmarketing study to fulfill the requirements for accelerated approval. This study has two parts. Part 1 is the optimal dose-finding study and Part 2 is a randomized phase 3 study. BEL 301 will enroll patients with newly diagnosed PTCL who have not been previously treated.

In Part 1, study treatment will be randomized in 5 arms, belinostat at 600- or 1000-milligram per meter squared plus CHOP; pralatrexate 20 or 30 milligrams per meter squared plus COP; or the standard of care, which is CHOP alone. Analysis will be done when 25 patients have received their planned treatment cycles to evaluate

safety and efficacy.

In Part 2, patients will be randomized into one of three treatment groups. In Group 1, patients who've received belinostat at the dose determined from Part 1 plus CHOP; in Group 2, patients who've received pralatrexate at the dose determined from Part 1 plus COP; and then Group 3 will receive the standard combination CHOP chemotherapy. The cycles will be repeated every 21 days for up to 6 cycles.

Let's look at the endpoints. The primary endpoint for Part 1 is to identify one of 2 dose levels, each for belinostat and pralatrexate that is optimal in combination with chemotherapy for Part 2. The recommended dose to take forward into Part 2 will be based on safety and efficacy, specifically the overall response rate of 3 months. Other parameters will include pharmacokinetics and exposure-response relationship.

In Part 2, our primary endpoint will compare the PFS of patients treated for up to 6 cycles with belinostat plus CHOP or pralatrexate plus COP to

CHOP alone. The secondary endpoints will include overall survival, ORR, and treatment compliance. And we will also capture exploratory endpoints of dose intensity, duration of response, and proportion of patients receiving the stem-cell transplant. Safety profiles will also be compared.

The study will be periodically evaluated with the Independent Data Monitoring Committee or IDMC. The IDMC will consist of two clinicians and one biostatistician that will periodically review patient-level efficacy and safety data. The IDMC will have planned meetings that include a data review at the end of Part 1. This will occur after 75 patients have been enrolled within the 3-month data. The periodic review meetings will be held 6 months after the first patient is enrolled in Part 1 and after each additional 100 patients are enrolled in Part 2. They will also meet annually. The committee will be responsible to recommend study continuation or discontinuation. There will be two planned analyses, one at the end of Part 1 and the second one after 120 PFS events have

occurred in Part 2.

Here we see the key statistical considerations. Part 1 of the study will enroll 75 patients for 15 patients per treatment and is expected to last for 24 months. Part 2 will not include patients or data from Part 1 and will enroll a total of 429 patients. As references for assumptions, we used the recently completed phase 3 study design using CHOP that had the same eligibility criteria and enrolled similar subtypes of PTCL. With a hazard ratio of 0.7, we are targeting a 30 percent improvement in PFS, improving from 10 to 14 months. The sample size was calculated to provide the statistical power for two pair-wise comparisons of combination versus CHOP with 80 percent power, a one-sided type 1 error rate of 2.5 percent, and a drop-off rate of 10 percent. This corresponds to 126 events in each of the treatment arms and 127 events in the control arm, for a total of 379 PFS events.

In summary, the confirmatory study 301 will be one of the largest randomized studies to date,

capturing the heterogeneity of PTCL and treatment-related outcomes. The study design was based on discussions with FDA. This includes dose optimization in Part 1, followed by the confirmatory study of clinical benefit in Part 2. The IDMC will review safety and efficacy at regular intervals. I'm excited to participate in this study as an investigator at MD Anderson, one of the participating study sites. Let me return the podium to Dr. Anvekar to explain the timelines and actions to support a timely completion. Thank you.

Applicant Presentation - Ashish Anvekar

MR. ANVEKAR: Thank you, Dr. Iyer.

The phase 1 studies indicated a meaningful ORR response for the combination regimens and we are eager to see if the results are reproducible in the confirmatory study. We believe we have put in the planning and the resources, and are moving with a sense of urgency while recognizing the challenges of completing a trial in this rare disease.

With that, I'd like to present the study timeline and provide some details on the study

execution. This is our projected timeline. It is important to note two things. One, the total duration of Part 2 is 4-and-a-half years to get the top-line PFS for all 379 events. This is in line with the expectation for a study in this rare indication, as well as prior studies conducted for romidepsin plus CHOP and brentuximab plus CHP. Further, for Part 2 of the study, our approximately 100 sites, which have been targeted, will be active at the same time. Thus, there should be no or minimal ramp-up needed in patient enrollment.

Two, the trial has interim time points where results will be available, indicating whether the active arm has benefit or not as assessed by the IDMC, the sponsor, and the FDA. The first such interim point is around December of 2025. An interim PFS analysis for the first 120 events should be available by February of 2028 and the final PFS results should read out in March 2030.

Acrotech has appointed a highly experienced CRO with a strong global presence that knows how to conduct and complete clinical studies. They have

strong oncology experience that spans 138 studies across 5,000 sites worldwide, involving more than 18,000 patients. Specifically, they have conducted 40 lymphoma studies over the past 5 years, including four PTCL studies. This experience gives us the confidence with our recruitment efforts and the ability to complete Study 301.

This slide shows the countries identified as the most likely to quickly and successfully enroll the target population for Study 301. This is based on data-driven analysis by our CRO that includes factors such as access to experienced sites, operational considerations, and prevalence of PTCL. The countries colored in red and orange have the highest disease prevalence and the trial experience and we have selected sites within those countries for participation. Study 301 is proceeding as planned. The CRO has screened the relevant sites and we currently have 77 sites in 10 countries that have agreed to participate to date.

We are working on regulatory approval of the protocol at a country and local level for these

sites. The agreed-upon protocol was approved by the central IRB in August 2023 in the U.S. We are happy to report that the first site was initiated in the U.S. in October 2023. Our aim is to enroll patients in a timely manner and target at least half of the patients to be from U.S. and Canada. Our confidence on the ability to enroll stems from a detailed analysis of the site capabilities, benchmark analysis done by our CRO, and the historical precedent from other PTCL conducted studies. We estimate an enrollment rate of 0.14 to 0.21 patients per site per month. This means we will finish the recruitment of Part 1 in 18 months and Part 2 in 21 months.

We are considering potential strategies to shorten the timeline for the currently agreed-upon PMR study. Specifically, we are looking to check the feasibility of increasing the number of sites to shorten the enrollment timeline. We are maintaining constant contact with high potential sites who may have currently not agreed to participate because of resources used, and to get

back to them and see if we can encourage participation in the trial by providing the resources required. We believe the best course is to continue with the agreed trial design and do not pursue any other indication, including relapsed/refractory PTCL. Of course, our focus is to implement strategies and tactics that can speed up the enrollment in the agreed-upon design.

For pralatrexate, the phase 1 study in patients with hepatic impairment is targeted to be completed by December 2024. The phase 3 study is already active. As early as December 2025, we could get interim results informing us of the utility, or not, of these products. We are eager to confirm if the encouraging results seen in the phase 1 studies are reproducible in the confirmatory trial in the first-line setting. We are confident on the study design and the execution plan while appreciating the challenges of the trial in this rare disease. Thank you for your attention, and we look forward to the discussion and your guidance.

DR. CHEN: Thank you.

We will now proceed with the FDA presentation from Dr. Kasamon.

FDA Presentation - Yvette Kasamon

DR. KASAMON: Hello. I'm Yvette Kasamon, a hematologist/oncologist and clinical team leader in FDA's Division of Hematologic Malignancies II. I will provide additional FDA perspectives on the prolonged accelerated approvals of pralatrexate and belinostat for patients with relapsed or refractory peripheral T-cell lymphoma.

The members of the FDA review team are listed here. My presentation represents their collective input. There are a number of important considerations regarding the prolonged accelerated approvals of pralatrexate and belinostat with delayed verification of benefit. I will discuss regulatory considerations and history and the delays in meeting milestones for postmarketing requirements. I will then discuss dosing and toxicity concerns with both products as they relate to the timeline for fulfilling postmarketing

requirements. Lastly, we will use this experience to foster a discussion on promoting timely verification of clinical benefit of these and other oncology products granted accelerated approval.

I will first highlight regulatory considerations with these two drugs. Pralatrexate and belinostat were both granted accelerated approval as single agents for the treatment of adult patients with relapsed or refractory peripheral T-cell lymphoma. Pralatrexate, a dihydrofolate reductase inhibitor, was approved 14 years ago based on a response rate of 27 percent, with durability in a single-arm trial in 109 patients with relapsed or refractory PTCL. Belinostat, an HDAC inhibitor, was approved 9 years ago based on a response rate of 26 percent, with durability in a single-arm trial in 120 patients with relapsed or refractory PTCL.

For products receiving accelerated approval, confirmatory trials to verify and describe the anticipated clinical benefit must be performed with due diligence; however, clinical benefit has not

yet been verified for either drug. As I will detail, the final protocol for the confirmatory trial was submitted to the FDA after a 7-year delay and the final report of the trial is not projected to be submitted until 2030, resulting in a total period of vulnerability of at least 21 years for pralatrexate and at least 16 years for belinostat.

The endpoints of response rate and the duration of response carry uncertainty in predicting clinical benefit in patients with lymphoma. There can be a lack of correlation between these early endpoints and survival outcomes, including in trials in patients with lymphoma. This discordance is more likely in settings where the product has a modest magnitude of effect on the early endpoint, especially in the context of significant toxicity. Pralatrexate and belinostat both have modest efficacy in patients with relapsed or refractory PTCL and notable toxicities.

The sponsor has cited a number of supportive studies for pralatrexate; however, the single-arm

supportive evidence is based on trials from a single region and relies on response rate and durability, measures that may predict clinical benefit. An agreed-upon phase 3 trial to confirm clinical benefit has yet to be completed. Any claims regarding confirmation of efficacy, which the sponsor has suggested for pralatrexate based on the randomized LuMIERE trial or a cited case control study, are inappropriate to apply to regulatory decisions. Rather, a well-controlled randomized trial, or trials, are needed to verify the anticipated clinical benefit for pralatrexate and belinostat.

For products granted accelerated approval in the relapsed or refractory disease setting, the confirmatory trial may be conducted in an earlier line and may evaluate the product as a single agent or as part of a combination regimen. If the confirmatory trial verifies clinical benefit, FDA would typically grant traditional approval for the new indication and for the indication under accelerated approval.

This table summarizes FDA-approved treatments for patients with relapsed or refractory PTCL. Each of the four drugs was granted accelerated approval based on response rate in a single-arm trial. Of the four drugs, two had confirmatory trials completed as required. For brentuximab vedotin, the confirmatory trial verified clinical benefit, leading to traditional approval. For romidepsin, the confirmatory trial failed and the commercial sponsor voluntarily withdrew the PTCL indication for romidepsin.

These are examples of the accelerated approval program working as it was designed, with an initial accelerated approval based on an early or intermediate endpoint followed by a confirmatory trial that either verified the anticipated clinical benefit, resulting in traditional approval, or failed to verify the clinical benefit, resulting in the product being withdrawn from the market. We recognize that pralatrexate and belinostat are outliers in the accelerated approval program.

As Dr. Mehta and Dr. Richardson stated, we

continue to assess the current therapeutic landscape when evaluating prolonged accelerated approvals. In patients with relapsed or refractory PTCL, a high unmet need continues. Brentuximab vedotin applies only to a subset of patients with relapsed or refractory PTCL and is also approved as part of first-line treatment. The primary aim of today's meeting is to discuss approaches to improving the verification of clinical benefit for these products and other products under accelerated approval, rather than the continued marketing or removal of pralatrexate and belinostat.

The experience with romidepsin in PTCL is important for today's discussion and illustrates a lack of translation of response rate to survival outcomes. Romidepsin, an HDAC inhibitor, received accelerated approval for PTCL based on durable response rates similar to those of pralatrexate and belinostat. The confirmatory trial for romidepsin was a randomized, open-label, phase 3 trial, evaluating romidepsin plus CHOP, or Ro-CHOP, versus CHOP alone in patients with previously untreated

PTCL. The trial failed to demonstrate statistical significance of its primary endpoint of progression-free survival. The overall survival curves were also similar, as were the response rates and depth of response. Moreover, the Ro-CHOP combination was associated with significantly higher toxicity, including grade 3 or higher toxicities, which included febrile neutropenia and cytopenias.

Notably, the addition of romidepsin resulted in the lower average relative dose intensity of cyclophosphamide, doxorubicin, and vincristine, suggesting that the addition of romidepsin could compromise delivery of the chemotherapy backbone. The experience with romidepsin highlights the need both for verification of benefit and minimizing the period of vulnerability, as the confirmatory trial failed and there was concern for increased toxicities in combination. The sponsor for belinostat and pralatrexate is planning to conduct a similar trial in the same population.

I will next summarize the regulatory history

for pralatrexate and belinostat. Before the accelerated approval of pralatrexate in patients with relapsed or refractory PTCL, the application was discussed at an ODAC meeting. The ODAC meeting was held in 2009 to discuss the clinical significance of the response rate and duration of response in the single-arm, phase 2 trial and the benefit-to-risk ratio for pralatrexate treatment. Limitations of the application were discussed, and the committee was asked whether the response rate and duration of response results were reasonably likely to predict for clinical benefit. The majority of the committee voted yes with four voting no.

The initial confirmatory trial PMRs for pralatrexate were released due to feasibility concerns. One was a randomized trial of maintenance treatment with pralatrexate in previously untreated patients with PTCL after response to first-line therapy. This trial was started but had poor accrual. The other randomized trial, which was not initiated, would compare

pralatrexate plus systemic bexarotene versus bexarotene alone in patients with refractory cutaneous T-cell lymphoma.

New accelerated approval PMRs were issued in 2014. The sponsor proposed the same confirmatory trial for both drugs, belinostat plus chemotherapy, versus pralatrexate plus chemotherapy, versus CHOP alone in patients with previously untreated PTCL. Because the trials involved combination regimens, dose-finding PMRs were necessary. The dose-finding PMRs were to establish the optimal and safe dose of each drug in combination with CHOP through separate phase 1, dose-finding trials in patients with PTCL. A sufficient number of patients were to be enrolled to characterize safety. The PMRs for the confirmatory trial are shown here with the original milestone dates. I will next summarize the design.

The agreed-upon protocol for the confirmatory trial has two parts. Part 1 is a randomized dose optimization phase comparing belinostat at two dose levels in combination with CHOP, pralatrexate at two dose levels in

combination with COP, and CHOP alone. Part 2 would be the confirmatory randomized trial comparing belinostat plus CHOP, versus pralatrexate plus COP, versus CHOP alone, using the selected dose levels in the dose optimization phase. The primary endpoint is progression-free survival per investigator with key secondary endpoints that include overall survival. Part 1 of the trial opened to accrual in October 2023.

Before discussing further details of the PMRs, I'll outline the regulatory history with respect to product ownership. The transfer of ownership of the pralatrexate and belinostat NDAs is summarized here, with the current sponsor acquiring both drugs in 2019. Of note, the transfer of product ownership should not result in delays since the new owner assumes responsibility and accountability for all outstanding regulatory requirements; however, there are multiple notable delays in the accelerated approval PMRs and safety PMRs as well.

The status of the accelerated approval PMRs

is shown here. Although the dosing PMR for belinostat plus CHOP was fulfilled on time, the final report for the pralatrexate-CHOP, phase 1 trial was submitted more than 5 years late. The final protocol for the confirmatory trial was submitted approximately 7 years late. I will discuss some reasons for these delays later in the presentation.

This slide compares the original milestone dates for the confirmatory trial and the most recent milestone dates proposed by the sponsor. The final protocol, which was to be submitted in late 2015, was submitted in early 2023. The final report, originally due in 2021, is currently projected to be submitted in 2030. There were also notable delays in safety PMRs for both drugs, as summarized here.

The report of a pralatrexate safety study in renal impairment was submitted approximately 2-and-a-half years late, and the report of a required safety study in hepatic impairment is outstanding and currently approximately 2 years

late. Other required safety studies with delays of more than one year are shown here, with delays up to 7 years. The recurrent delayed milestones for these PMRs warrant a close inspection of the reasons and how these delays can be mitigated.

There are a number of important considerations regarding safety and dosing for both pralatrexate and belinostat. It's important to have confidence in the dose, whether it's as monotherapy or as part of a combination regimen. Originally, the goal of dose selection for both pralatrexate and belinostat as monotherapy was to determine the maximum tolerated dose or MTD. In both cases, dose escalation studies began in patients with solid tumors, and studies in patients with hematologic malignancies were subsequently started at doses close to the MTD based on data from the solid tumor trials.

In the studies conducted in patients with hematologic malignancies, the MTD, outlined in red, was reached fairly quickly with very few patients enrolled at lower dosages. Consequently, there was

limited data to assess whether lower doses may have provided adequate efficacy with lower rates of adverse events.

A closer look at the data for both drugs showed that high exposures were not associated with better outcomes. This is, in part, because of limitations of the data. Positive exposure-response relationships for safety were observed for pralatrexate, suggesting that high exposures were associated with higher rates of adverse events such as thrombocytopenia. For belinostat, while no relationships were observed between exposure and safety events, the assessment is limited by patient numbers and the limited duration of exposure.

The sponsor has contended that pralatrexate as monotherapy is overall well tolerated in the majority of patients with PTCL; however, there are notable toxicity concerns with pralatrexate. The most common any grade and grade 3 or 4 toxicities are hematologic toxicities and mucositis. Both are included as warnings and precautions in the U.S.

prescribing information. In the pivotal phase 2 trial, there were high rates of serious adverse events, dose modifications, and discontinuations. A leading toxicity was mucositis, affecting 70 percent of patients, with 21 percent developing grade 3 or 4 mucositis. Other common adverse events affecting at least 21 percent of patients included cytopenias; gastrointestinal toxicities; edema; cough; and epistaxis. The FDA review staff concluded that there was insufficient data available to determine if the dose was optimized in terms of efficacy and safety or whether lower doses might be better choices.

For belinostat, the total duration of treatment was short, a median of 7 weeks, and grade 3 or 4 AEs occurred in 61 percent of patients. Although the AEs may be manageable, it remains unclear whether a lower dose of the belinostat may be equally efficacious with lower rates of toxicity, as was noted in the clinical pharmacology review of the NDA.

Because of the dosing concerns and

uncertainty with each agent as monotherapy and the lack of evaluation of these agents in combination with chemotherapy, dosing PMRs were issued for each drug in combination with CHOP. These evaluations in combination were completed by the sponsor, but concerns remained based on FDA review of the data.

For both products, dose exploration in combination with CHOP was also limited, prioritizing an MTD approach. For pralatrexate, although a good number of doses were assessed, there were too few patients enrolled between 10 and 25 milligrams per meter squared to evaluate the efficacy and safety well. The response rates ranged from 100 percent at 10 milligrams per meter squared to 84 percent at 30 milligrams per meter squared, and the grade 3 or 4 event rates ranged from 70 to 100 percent. Similar observations were made for belinostat, where only 2 doses were assessed in a few patients per cohort. The response rate of both doses was 86 percent and the AEs were similar.

Recently, the FDA further questioned the

doses selected for combination therapy. FDA determined that there was a need for further dose optimization for both drugs when combined with chemotherapy before pursuing a confirmatory trial in the first-line curative intent setting. In early 2023, the sponsor and the FDA agreed on these dose exploration plans. Continued pursuit to identify a safe and optimal dose for both drugs is in line with the Oncology Center of Excellence's Project Optimus.

The toxicity profile of pralatrexate and belinostat, coupled with their modest efficacy in single-arm trials, underscores uncertainty in clinical benefit. We acknowledge that in some cases, durable response rates in single-arm trials have supported traditional approval in settings where randomized-controlled trials would be impracticable; however, it is feasible to conduct well-controlled randomized trials in patients with PTCL in reasonable time frames.

Examples include the romidepsin CHOP trial, where approximately 7 years elapsed from trial

initiation to primary completion, and the pivotal trial of brentuximab vedotin in patients with previously untreated PTCL. Approximately 5 and a half years elapsed between that trial initiation to primary completion despite the trial being restricted to a subset of PTCLs, namely those with CD30 expression.

Here we have reviewed the delays in meeting milestone timelines for pralatrexate and belinostat, including delays from meeting further dose optimization and delays for administrative reasons. I will next briefly outline some potential approaches to promoting more timely verification of clinical benefit.

Accelerated approval is a dynamic situation, and we continually learn from past experiences. This experience affords an opportunity to consider potential strategies to minimize delays in confirmatory trials for future accelerated approvals, as we have tools to help navigate these challenges.

What could have been done better on the

sponsor side and the FDA's? First, the sponsor cited administrative reasons for delays, namely the transfer of product ownership of pralatrexate and belinostat. As mentioned, the new owner of a product assumes responsibility and accountability for all outstanding regulatory requirements. Additionally, PMR milestones are agreed upon by both the sponsor and FDA. If the sponsor anticipates potential delays in meeting PMR milestones, more interactions with FDA should be sought, whether following transfer of NDA ownership or at any appropriate point in the drug's development. This would allow a further understanding of the issues and allow for a collaborative approach to mitigate these delays.

With regard to adequate evaluation of dose, there was delay in the conduct of the dose-finding trial of pralatrexate plus CHOP and delay in FDA feedback on the need for additional dose optimization. There is a more recent focus on dose optimization earlier in drug development. Adequately evaluating dose has always been a

priority; however, through Project Optimus, there is a renewed interest and greater transparency regarding the need for adequate dose evaluation prior to conducting registration trials.

Project Optimus was initiated by the Oncology Center of Excellence to focus on better dose selection in oncology. MTD-based dose selection evolved from cytotoxic therapies, where it was difficult to determine an efficacious dose with little toxicity. This paradigm has been applied ubiquitously, even to newer more targeted therapies. Consequently, for many drugs the dose is too high, as evidenced by high rates of adverse events; dose reductions; interruptions; and discontinuations observed in oncology. Project Optimus is an initiative to encourage dose selection that balances efficacy and safety more by incorporating greater use of nonclinical data; pharmacokinetic and pharmacodynamic data; modeling and simulation; and evaluation of efficacy and safety at lower dose cohorts with more patients.

Additionally, the Oncology Center of

Excellence has a focus on multiregional trials that may help promote timely completion of trials. The focus is on ensuring that clinical trials have broad representation of diverse patient populations from multiple regions globally. Ensuring clinical trial sites from broad regions might help expedite drug development, especially for rare diseases.

Recent updates to accelerated approval legislation may also promote timely verification of clinical benefit. In December 2022, Congress passed the Food and Drug Omnibus Reform Act, or FDORA, which allows the FDA to require that confirmatory trials be underway prior to approval. As mentioned previously, it also allows the FDA to require submission of progress reports on the confirmatory trials every six months. This helps track the status of the trials and identify delays earlier that may be actionable. As mentioned, we continually learn from past experiences, and these additional authorities granted by the new FDORA legislation were informed by such experiences.

As I have summarized, pralatrexate and

belinostat have had notably prolonged accelerated approvals with delayed verification of benefit, with various factors contributing to that delay. With this in mind, we would like for the committee to discuss the following two topics.

First, please discuss the delays in post-approval confirmatory trials for pralatrexate and belinostat, and whether the current plan to verify the clinical benefit of these products in patients with peripheral T-cell lymphoma is reasonable, considering the sponsor's proposed timelines. Additionally, please discuss strategies to promote timely completion of the confirmatory trial for pralatrexate and belinostat and insights from this experience that may facilitate completion of confirmatory trials for future accelerated approvals. As previously mentioned, there is no voting question for today's meeting. We look forward to the committee's insights on these important topics. Thank you for your attention. This concludes my presentation.

Clarifying Questions

DR. CHEN: Thank you, Dr. Kasamon.

We will now take clarifying questions for Acrotech and the FDA. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon again after you have finished your question. When acknowledged, please remember to state your name for the record and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and any follow-up question with, "That is all for my questions," so we can move on to the next panel member. Thank you.

DR. ADVANI: Thank you. I'm Dr. Advani from Stanford. I have a question for the sponsor. I may have missed it, but the pralatrexate-CHOP was the combination on that study, but your study design for the confirmatory trial is COP not CHOP, so I was a little confused about that. The second

question I had was, when you say standard of care CHOP, you didn't show the eligibility criteria. Are you excluding ALCL? Because I think there, whether it's ALK-positive or ALK-negative, the standard of care would not be CHOP; it would be brentuximab and CHOP.

So I'm just trying to get some clarification on the study design as to why COP, and are you going to exclude ALCL because otherwise, CHOP would not be a standard of care for ALCL. Thank you.

MR. MINGMONGKOL: Sure. So first, just to introduce myself, I'm Paul Mingmongkol. I'm a senior director at Acrotech, and I'm here to bring our panel in to answer your questions. For both of your questions, I'd love to bring up Dr. Iyer.

DR. IYER: Thank you, Dr. Advani, for that question. The rationale at the time of the study design, and it was submitted and discussed, was that the pralatrexate and Adriamycin are overlapping toxicities to make sure that pralatrexate is not under-dosed and to maintain the dose intensity. That was one of the suggestions,

but this is definitely for the Part 1 and could be revisited for Part 2. As far as your second question, ALCLs are not part of this because there is a very good option with brentuximab.

DR. CHEN: Thank you.

Dr. Gradishar?

DR. GRADISHAR: Hi. Dr. Bill Gradishar from Northwestern, and this is to the FDA. I had a question. I appreciate the history of the drug development and the challenges that were described by both presentations, but I guess the question I have is thinking about having sat, as many of us, on DMCS and participated in trials where expected versus actual accrual are very different lines, with oftentimes a big separation between them.

I still am not clear what the carrot and stick is to move this along. Is that going to be placed with certain timelines? And then, what are the implications if the timelines aren't being met? That's that's my question. Thank you.

DR. KASAMON: This is Dr. Kasamon. If there are anticipated delays, there needs to be

communication across stakeholders so there can be completion of this trial in a timely manner. We're committed to supporting completion of the confirmatory trial in an expeditious manner, as evidenced by the discussion topics for today's ODAC meeting. As mentioned, with FDORA, there is more transparency in the progress of monitoring the confirmatory trial, so the FDA welcomes working with the sponsors and fostering a collaborative approach to mitigate delays. Thank you.

DR. PAZDUR: Dr. Gradishar, this is Rick Pazdur. I think you hit a central element here, and that's why we are really emphasizing that these trials be ongoing and near completion. We have very little authority at this time, other than removing a drug from the market, so this poses a problem where patients are in the middle of this, so to speak, and we really want to do the right thing for patients and not deny them a potentially -- and I underline the word "potentially" -- effective therapy here. But we have very limited power once it comes to the drug

is on the market, other than while we're waiting for these confirmatory trials, what to do here, other than removing it because they have not demonstrated due diligence. And then who's in the middle here? The patient; and this is what is quite unfortunate. And that's why we have been big advocates that these trials need to be ongoing here.

DR. GRADISHAR: Thank you.

DR. CHEN: Thank you.

Dr. Spratt?

DR. SPRATT: Thank you so much. I appreciate everyone's presentations. A comment and a question, and I'll direct one question to the FDA and one to the sponsor. At least from my vantage point, I think that I view an accelerated approval as something that if that pathway did not exist, this, off of a single arm, a relatively small trial, would be unlikely to gain a traditional approval. So this is something that has been granted, so it's almost like I sometimes view this as a loss to take something away that you never

fully had.

I think that as we saw with the romidepsin -- and there's plenty outside of these disease-based stories -- that we often -- and I use this carefully, and I say this -- we punish patients by having aggressive disease by thinking we need to give them more therapy when we haven't proven that therapy works, because us as physicians feel we need to do something because it's a lethal and aggressive disease. So I think that we have seen in this disease space, despite it being a rare disease, that we can harm patients even when you see something that, say, has biological activity.

The question to the FDA is, it was stated in the slides, an accelerated approval, in quotes, "is based on an effect on a surrogate endpoint that's reasonably likely to predict clinical benefit," unquote. Objective response rate is not, by the data that has been shown or on literature review, a surrogate endpoint in this disease space, or even in potentially a larger broader category, in non-Hodgkin's lymphoma.

I didn't see any data presented in either presentations on this being a surrogate for either quality of life or on survival; obviously, in the trials, romidepsin and alisertib, it clearly is not. So I think we are misusing the terms of "surrogacy" in a correlative or prognostic endpoint, and, obviously, these interim endpoints, intermediate endpoints, are correlative, but they're not necessarily reaching a bar.

So the question is, can an established threshold of surrogacy, often termed a "surrogate threshold effect," be established for something like objective response rate or PFS for this proposed randomized trial so that we set a bar to move past that phase 1 design?

DR. RICHARDSON: Hi. This is Nicholas Richardson, FDA. Thank you for the questions, Dr. Spratt. You raise a number of topics that are important. Regarding endpoints, I'd like to ask Dr. Mehta to comment to start.

DR. MEHTA: Yes. Thank you. Can we have slide number 82 pulled up?

I think you raised an important point about surrogate endpoints. We define surrogate endpoints using the Prentice criteria in oncology, and for an endpoint to be a true surrogate, it has to have a direct 1 to 1 -- I believe 81 in the slide deck, not the number. This might be one slide before that. I apologize. But this presumes a 1-to-1 relationship between that clinical endpoint and survival, and we do not have that, so we tend to not use this term "surrogate endpoint."

If we could move to slide 78, so three slides earlier. Actually, in the accelerated approval legislation -- and I'm glad you brought up this point because it's important to point this out -- we can approve a product for accelerated approval based on either a surrogate endpoint that is reasonably likely to predict clinical benefit or a clinical endpoint that could be measured earlier than either morbidity or mortality, which is reasonably likely to predict that clinical benefit. So in some of these cases, we're relying on overall response rate as an endpoint that's measured

earlier than morbidity or mortality.

DR. GORMLEY: This is Nicole Gormley, division director. I'd like to just highlight as well. You bring up a really important point in that we have seen, as well, in a lot of our trials some discrepancy and discordance between these earlier intermediate endpoints that we use, and then ones that we know are established and important, like overall survival. And to that end, this trial, the proposed confirmatory trial, has a progression-free survival endpoint but then also has overall survival as a secondary endpoint, and for our regulatory review, it will be really important to have confidence in those overall survival results.

Even when we rely on earlier endpoints -- overall response rate, progression-free survival -- at the FDA, we always evaluate overall survival because of its importance and its ability to serve as both an efficacy endpoint and as a safety endpoint, so this confirmatory trial will have an assessment of

overall survival as well. Thank you.

DR. CHEN: Thank you.

Dr. Vinks?

DR. SPRATT: If it's ok, I had a question for the sponsor as well. The question for the sponsor is, I keep hearing one of the drivers of the delays is this is a rare disease, so while, obviously, far more rare than many cancers, it's clearly more common. I think all of pediatric malignancies combined is around 17,000 cases, plus or minus a year, and that's numerous cancer types, and obviously many, many randomized trials are conducted within it. The proposed trial that you're conducting between the phase 1 stage and stage 2 stages are over 500 patients.

So I guess, is this really the rarity of the disease given the trial you're proposing, if it's feasible to conduct, or is it these other logistical challenges regarding the company being bought and exchanged multiple times?

MR. MINGMONGKOL: Let me invite Dr. Anvekar to answer your question.

MR. ANVEKAR: Let me answer it in a two-fold. One is the PTCL, as we indicated, is a rare disease, and therefore we have also looked at the trial completion from a global perspective so that the enrollment rate is as per our forecast. But the ability to diagnose the patients of PTCL, that I will maybe point out to Dr. O'Connor to present in terms of there are 10[000] or 15,000 cases in a year, and if there are 10 [000] or 15,000 oncologists in the U.S., maybe one patient per doctor is seen, and therefore the ability to diagnose that patient and be able to channel it to our study is also equally important.

So why we feel very confident about working with our CRO and the enrollment rates, and the projected timelines are in line with the romidepsin plus CHOP and the brentuximab plus CHP study, which has been done, from that perspective, we feel very confident. Thank you.

DR. CHEN: Thank you.

Dr. Vinks?

DR. VINKS: Yes. Thank you. Thank you to

the presenters for their informative presentations. I'm Alexander Vinks. I'm with NDA Partners. As a clinical pharmacologist, one of the things that I'm very interested in hearing is dose optimization. I just have a couple of clarifying questions for the sponsor, as there is a dose optimization part 1 in the proposed phase 3 trial. I'm just interested to hear what has been learned from the previous dose-finding studies, where a more traditional approach of maximum tolerated dose was used as opposed to what in our field now is modeling for precision dosing approaches and modeling and simulation used to look at exposure rather than dose, and then link that into, say, pharmacodynamic markers, and used that as the exposure-response relationship to be studied and analyzed.

So I was just wondering if any of the modeling and simulation approaches that are currently commonly used, especially also in areas outside of oncology and have been basically highlighted through Project Optimus, whether the sponsor has used or will be using this as part of

the dose optimization part. Because one of the concerns I would have is whether there's a true difference in exposure between a 20- and a 30-milligram per square meter dose or variability between patients in terms of pharmacokinetic behavior, and therefore exposure could be extreme in that you have overlapping distribution or exposure, so therefore, there is no, quote/unquote, "dose effect" to be discerned. I'll stop there.

MR. MINGMONGKOL: To answer the historical question, I'm going to ask Dr. O'Connor, and then I'll turn it over to Dr. Iyer, who will take the second part of your question.

Dr. O'Connor?

DR. O'CONNOR: You raise some important and interesting questions about how we're finding the dose to move forward in the recommended phase 2. Back in the days when at least the PROpel study was planned and implemented, there was no Project Optimus and/or theories about dose exposure were probably far more primitive. I will say, though, that at the time, we did collaborate with various

pharmacokineticists and did do an extensive population PK modeling experience that we tailored to the lymphoma patients.

You may or may not recall, but the early phase 1 experiences with the drug in solid tumor actually escalated the drug all the way up to 150 to 200-milligram per meter squared, and there was actually a lot of that population PK modeling that we implemented that knocked us down to doses around the 20-to-30-milligram per meter squared range. Back then, yes, MTD was and had been the criteria used to identify the dose that moved forward in the recommended phase 2 studies, but we didn't have the benefit of all the modeling, exposure data, and instruments that we have today. So I think we made a pretty good effort back then to try to implement the tools at our exposure to try and explore these issues in detail.

With regard to the phase 3, I'm going to hand it off to Dr. Iyer.

DR. IYER: Thank you for the question. So in the upcoming and ongoing study, there is the

mandate to look at not just the dose finding but also to include PK sampling and analysis that PK data are sufficient quality and quantity for characterization of the various population PK modeling such as linearity, absorption, et cetera. So there is going to be limited PK sampling in patients, particularly in the U.S., who are willing to participate, and also includes Canada. And all patients will go on the pralatrexate-COP or belinostat-CHOP at various time points, and that will help us guide the decision making for the Part 2. It also includes certain pharmacodynamic endpoints such as H4 acetylation and DNA methylation.

DR. VINKS: Thank you.

DR. CHEN: Thank you.

In the interest of time and schedule, we will have to break here. We will be taking a 10-minute break. We have noted the panel members who have outstanding questions, and if there is time at the discussion section, we will certainly circle back to your questions at that point. So we

plan to restart in 10 minutes from now, which would be at 10:50. Thank you.

(Whereupon, at 11:39 a.m., a recess was taken, and meeting resumed at 11:50 a.m.)

Open Public Hearing

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

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the applicant. For example, this financial information may include the applicant'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 chair. Thank you for your cooperation.

Speaker number 1, please unmute and turn on

your webcam. Will speaker number 1 begin and introduce yourself? And please state your name and any organization you're representing for the record.

MS. PHILLIPS: Hello. I'm Sophia Phillips, a health policy associate at the National Center for Health Research. Our scientists and health professionals scrutinize the safety and effectiveness of medical products, and we don't accept funding from companies that make those products; therefore, I have no conflicts of interest.

We thank all of you for participating in this meeting to publicly scrutinize the dangling accelerated approvals for pralatrexate and belinostat. Confirmatory trials for drugs granted accelerated approval are too often delayed for years, and are later shown to fail to demonstrate meaningful patient-centered outcomes. Meanwhile, the drug remains on the market and patients are paying for drugs that are not proven to benefit them. This is particularly unacceptable for these

two drugs, for which the sponsor does not expect to complete confirmatory trials for seven more years, in addition to the 14 years and 9 years that the drugs have already been on the market without clear evidence of a clinically meaningful benefit.

Oncology drugs account for more than 60 percent of all accelerated approval drugs, and we can all agree that the public has a right to question the lack of evidence regarding the benefits of these drugs. Research indicates that as of 2019, only 20 percent of cancer drug indications approved through the accelerated approval pathway, from 1992 to 2017, demonstrated improvements in patients' overall survival based on their confirmatory trial data. Our center's research also found no evidence of improved quality of life in most confirmatory trials.

In an analysis of 100 accelerated approval confirmatory trials completed or due between 2012 and 2021, more than half were past their expected completion deadline set by the FDA. Both pralatrexate and belinostat fall in that category.

As I previously stated, it has been more than 14 years and more than 9 years since they were awarded accelerated approval, respectively.

The FDA has stated that an appropriate target completion date for oncology products would ideally be no later than 2 to 4 years after accelerated approval is granted. Further, we agree with FDA that the reasons provided by the sponsor for the delay of these trials are not sufficient justification for these very long delays, so why are these products allowed to remain on the market?

This delay is not fair to patients, most of who assume these drugs are proven to have benefits that outweigh the risks. Unfortunately, in addition to clinical uncertainty about the benefits of these drugs, they often have serious adverse effects that result in high rates of discontinuation. For example, nearly 50 percent of patients taking belinostat experienced a serious adverse event. This includes the 10 percent that experienced cardiac-related adverse effects and 2 patients with cardiac failure. In addition to

neither drug being well tolerated by patients, these drugs are very expensive. Each cost hundreds of thousands of dollars annually, adding to the overall burden faced by cancer patients and taxpayers.

There are significant concerns in the accelerated approval program that must be addressed: the long delay before confirmatory trials are completed and made public; the lack of meaningful clinical data provided in confirmatory trials, which often continue to rely on unproven surrogate endpoints; and additional delays that keep drugs on the market even when confirmatory trials failed to confirm that the drugs are safe and effective. As a result of these issues, patients have been harmed by unproven products remaining on the market.

We urge the FDA to hold this sponsor and others accountable for their failure to conduct confirmatory trials in a reasonable timeline. While we support the new effort by the FDA to require confirmatory trials to start prior to

granting an accelerated approval, that does not affect these two drugs, and in the future, it does not provide an incentive for sponsors to complete confirmatory trials in a timely manner. As soon as a drug is approved, many study participants may drop out of trials due to fear of being placed in the placebo group unless the sponsor acts quickly to complete their trial.

In conclusion, when sponsors exploit the flexibilities granted by the FDA, as happened with this sponsor, we believe it necessary for FDA to rescind approval until a trial is completed that confirms meaningful clinical benefits. Thank you.

DR. CHEN: Thank you.

For the record, speaker 2 has confirmed that they will not be able to participate as a speaker today, so we will proceed to speaker number 3.

Speaker number 3, please unmute yourself and turn on your webcam. Will speaker number 3 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. GALASSO: Thank you to the committee for allowing me to make this statement on behalf of Dr. Steven Horowitz. My name is Natasha Galasso, and I'm the administrative director of the T-Cell Lymphoma Program at Memorial Sloan Kettering Cancer Center. Dr. Horowitz writes:

"I'm a medical oncologist and clinical translational investigator with a focus on T-cell lymphomas. My current title is Member at Memorial Sloan Kettering Cancer Center and Attending Physician at Memorial Hospital; Professor of Medicine at Weill Cornell Medical College; and I hold the incumbent known as Garden Foundation Chair at Memorial Sloan Kettering.

"At MSK, I direct the T-cell Lymphoma Program. I'm the founding and current chair of the NCCN committees on T-cell and cutaneous lymphomas. My practice is divided between the care of people with T-cell and/or cutaneous lymphomas and patient-based research, primarily focusing on identifying and studying new therapies for people with T-cell and cutaneous lymphomas. From these

roles and my experiences, I can attest that we desperately need new and better therapies for people with T-cell lymphomas.

"There are significant hurdles in developing therapies for rare diseases, including access to compounds, patient access, and access to funding. The accelerated approval program has benefited our patients and the physicians who care for them by allowing early access to effective therapies well in advance of a completed confirmatory trial. Many of our past and current patients have benefited from, and continue to benefit from, access to therapies such as romidepsin, belinostat, and pralatrexate, that gained approval through the accelerated approval program.

"The confirmatory trial process has been much less successful. We lost the label for romidepsin for people with relapsed and refractory T-cell lymphoma due to a negative confirmatory trial that tested romidepsin in untreated patients in combination with chemotherapy. At the time of the trial design, those investigators didn't know

that the most significant benefits for romidepsin are in people with certain subtypes of T-cell lymphoma, those with angioimmunoblastic or follicular helper T-cell lymphomas, as our group subsequently identified. The end results showed no benefit for the primary endpoint of progression-free survival overall, but a statistically significant benefit for the subset of those with follicular helper T-cell lymphomas.

"Nonetheless, the overall study was negative and the label was withdrawn, not due to any new information diminishing the efficacy or questioning the safety of romidepsin in the originally approved population of relapsed and refractory patients, but rather because the biology of the different types of T-cell lymphomas that impacted the efficacy of romidepsin was not known until later. However, there are rarely second chances to do a large study in a rare disease.

"The story of belinostat and pralatrexate is less of an, if I only knew then what I know now situation. By all measures, the confirmatory

studies were never moved forward with the commitment and resources needed to successfully complete in a timely fashion. I'm not here to justify, explain, or defend the choices made by the sponsors of new drugs, but to speak for the patients that I care for every day and the physicians who treat those with rare diseases.

"We need additional therapies for these patients, not only new treatments to be given instead of the current treatments, as would be determined by a randomized study. We need new treatments in addition to current treatments. These treatments can be effective in reducing and controlling often life-threatening diseases but they are not cures. When they fail to control disease or lose their efficacy over time, we need a next line of therapy, and a next, and a next to keep our patients safe.

"Equipoise would dictate that the needs of patients and the clinicians who care for them be considered in addition to assessing the actions of the sponsors in fulfilling their obligations. My

hope for the future is that we and others who are committed to this field will find many new treatments for our patients; however, right now T-cell lymphomas are not diseases for which we have multiple effective therapies that patients and physicians can afford to lose another or another. I ask that the cost to patients of regulatory actions in terms of available options, or lack thereof, be considered alongside the importance of following a rigorous regulatory process. Thank you."

DR. CHEN: Thank you.

Speaker number 4, please unmute and turn on your webcam. Will you begin and introduce yourself? And please state your name and any organization you are representing for the record.

MR. TALAMANTES: Hello. My name is Sonny Talamantes, and I was diagnosed with peripheral T-cell lymphoma in April 2017. That year, I endured a traditional chemo process and a bone marrow transplant using my own cells because I didn't have matching donors. In October 2018, the

cancer returned. I was told I had two options: chemo, which would likely result in a life span of approximately 24 months, or immune therapies with no guarantees. I selected the immune therapies.

I tried several types of therapies, none of which placed the cancer into remission. In 2021, I was offered belindodac [ph] [sic - belinostat], and with a bone marrow transplant, belinostat was a possible bridge for a cure or some other treatment options, which at that point did not exist. A few months later, my disease went into remission. At the time of this statement, I'd been in remission for over 2 years.

Unfortunately, I developed a secondary cancer of leukemia; however, a new search was done for a bone marrow donor finding a match. Belinostat was in fact the bridge I had hoped it would become. Today, I make this statement from the City of Hope, where I'm in the bone marrow transplant process. That is all I have to say, and thank you for your time.

DR. CHEN: Thank you.

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

DR. FOSS: Good morning. I'm Dr. Francine Foss, professor of medicine in hematology and cell therapy at the Yale University School of Medicine and head of the T-Cell Lymphoma Program. I have no conflict with the sponsor with regard to my presentation at this meeting.

I would like to thank the committee for the opportunity to speak. I'm voluntarily here today to represent the interests of patients with T-cell lymphoma. I've cared for patients with T-cell lymphoma for over 30 years, and as a translational researcher, I've participated in the registrational clinical trials for all of the drugs with full or conditional approval for T-cell lymphoma. Today, I'd like to present a real-world perspective on treatment patterns for T-cell lymphoma.

While much has changed over the 30 years of my practice, T-cell lymphoma remains an unmet

medical need. CHOP and CHOP-like chemotherapy regimens are the standard in the front line, but despite a reasonable response rate, most patients unfortunately relapse, and less than half of the patients, with the exception of ALCL, are alive at five years. So what are the prospects for cure or long-term remission for our patients in the real world?

Several years ago, the community of PTCL oncologists conducted a prospective registry study to examine treatments and outcomes for PTCL in the United States. This was called the Complete Registry and enrolled 500 patients. A similar prospective global registry study called the T-Cell Project was also conducted around the world and enrolled 1400 patients. Both registries reported similar poor outcomes for PTCL patients, with most relapsing after front-line therapy.

One poignant finding from these registries was that while the standard of care for patients who achieved a complete remission in the front line was to undergo consolidation autologous stem-cell

transplant, only 25 percent of patients with PTCL actually had a transplant. The other 75 percent, or the vast majority of our patients, have little or no chance of cure and remain in need of novel therapies.

For these relapsed and refractory patients, available novel agents, including belinostat, pralatrexate, romidepsin, and brentuximab vedotin, have shown activity and are meaningful therapeutic options for many. In fact, when we reviewed the relapsed and refractory patients in our complete registry, there was a surprising finding that those patients treated with single agents in the relapsed setting had a higher complete response rate than those who received standard chemotherapy, 41 percent versus 19 percent. And there was also increased median overall survival of 38 versus 17 months, favoring those patients who received the novel agents.

A worldwide retrospective study of over 900 patients with PTCL has recently been completed, and that will be presented by Dr. Salvia Jain from

Mass General at the upcoming American Society of Hematology meeting. In this study, 35 percent of the relapsed patients received novel agents rather than combination chemotherapy, and the results showed a statistically significant, progression-free survival advantage with the use of these novel agents, even in those patients who did not undergo a stem-cell transplant and irrespective of other important prognostic factors such as primary refractory status or lymphoma subtype.

Another finding from both registries was that single agents were as effective, or in some cases more effective, to put patients into meaningful remissions and thus bridge them to potentially curative stem-cell transplant. While these are clearly observational and not controlled clinical trials, the data from these real-world studies show that single novel agents are often used in lieu of combination chemotherapy in the relapsed and refractory setting and have resulted in similar, if not better, outcomes in terms of progression-free survival and overall survival,

thus defining in the real world the role that these single agents may play in our treatment algorithms for PTCL.

So how do these novel agents such as belinostat and pralatrexate benefit our patients? In the words of Rob, one of my long-term survivors who has remained on one of these agents now for several years, quote, "It is critical that patients with PTCL who have a dismal outcome have access to drugs which have demonstrated activity and that these drugs remain available to patients. Patients like myself often fail one or more agents and need these additional options," unquote.

Having these drugs available allows T-cell lymphoma physicians like myself to provide options to a large number of patients, especially those who are older, have comorbidities, or otherwise are not candidates for aggressive strategies or stem cell transplant.

DR. CHEN: Dr. Foss, I'm sorry to interrupt, but could you please wrap up? You're out of time.

DR. FOSS: Yes, one more sentence.

I speak for the community of PTCL oncologists in support of the ongoing randomized trials to confirm the activity of these novel agents and hope that they continue to be available to our patients. Thank you for the opportunity to speak.

DR. CHEN: Thank you.

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

DR. HAVERKOS: Thank you. My name is Brad Haverkos. I'm an associate professor at the University of Colorado. My clinical and research focus is on T-cell lymphomas. I've previously served as an advisor to Acrotech but am voluntarily here today.

As you all know, PTCLs are a rare heterogeneous group of malignancies with generally poor outcomes. Five-year survival for most subtypes with current therapies is around 20 percent, and there are currently only three

FDA-approved drugs for relapsed PTCLs: belinostat, pralatrexate, and brentuximab, and the latter drug, brentuximab, is now being used in front-line setting, so there are effectively only two approved considerations in the relapsed setting.

I want to re-highlight two important points to keep in mind as it pertains to both pralatrexate and belinostat. First, given the recent improved understandings of the molecular underpinnings of PTCLs, we're beginning to understand that depending on the specific PTCL subtype, responses are different between drugs. As an example, in the initial belinostat, single-arm, BELIEF trial, in relapsed patients, there seemed to be better responses in the specific subtype of T-cell lymphoma called angioimmunoblastic T-cell lymphoma. The subsequent accumulated data from clinical practice and retrospective studies show that this subtype of patients, which fall under the more broad heading of peripheral T-cell lymphoma with a follicular helper phenotype, do indeed respond better to histone deacetylase inhibitors. So while

there is modest overall response rate in PFS in the BELIEF trial as a whole, in clinical practice, most physicians favor using HDAC inhibition such as belinostat and relapsed PTCLs with a follicular helper phenotype, where there is a higher overall response rate and more meaningful duration of response in this subset.

Thus, I think there is little question in the minds of physicians who have focused and treat T-cell lymphoma about the safety and efficacy of belinostat in the relapsed setting, and with regards to the safety toxicity of pralatrexate, physicians have learned how to mitigate the GI toxicity that was observed in the initial clinical trial. Given this, as you all have acknowledged, belinostat and pralatrexate remain key treatment options for relapsed PTCLs.

The second point that I'd like to make, as you recognized, the biggest challenge and controversy surrounds the confirmatory trial for pralatrexate and belinostat. While certainly a confirmatory trial is feasible, there are likely to

be challenges to enrollment in the confirmatory trial. Namely, given the heterogeneity of PTCL and more favorable responses in specific subsets of PTCL, such as the patients with the follicular helper phenotype, there may be challenges to accrual given the potential, due to lack of enthusiasm, of enrolling to the belinostat arm for non-PTCL follicular helper subtypes.

While the future of PTCL treatment will almost certainly involve combinatorial treatment as proposed in the current confirmatory trial, comparing belinostat plus traditional chemo, versus pralatrexate plus chemo, versus chemo alone, an additional enrollment barrier may surround the lack of excitement to potentially enroll to a standard-of-care, chemo-alone arm. As reviewed by Dr. O'Connor, this lack of excitement for chemo alone is due to the historically poor outcomes of the chemo-alone, CHOP-like regimen, and this data has resulted in questions on what exactly is the best upfront treatment approach for PTCLs. And for this reason, NCCN guidelines, for which I'm a

writing member, list clinical trial and multiple different CHOP-like regimens as potential front-line treatment options. Thank you for your attention.

DR. CHEN: Thank you.

We will now move to speaker number 7. Speaker 7, please unmute and turn on your webcam. Will you begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. RENEAU: Good afternoon. My name is John Reneau. I'm an assistant professor of medicine at The Ohio State University. My clinical practice and my research also focus on treatment of T-cell lymphomas and the development of novel therapies for these diseases. In the interest of transparency, I have served as an advisor to Acrotech in the past, but I am voluntarily here today.

So thank you for the opportunity to speak to you today regarding my clinical experience using belinostat and pralatrexate and to express to you

my opinion that maintaining access to these drugs is important in the treatment of relapsed PTCL, at least currently. The epidemiology, prognosis, and treatment landscape of PTCL has been well outlined today by Dr. O'Connor, Dr. Foss, and Dr. Haverkos, as well as others, but I would briefly like to highlight and emphasize several important points.

The first is that despite the rarity of PTCL, there's a significant amount of biological heterogeneity under the umbrella of PTCL, leading to what is essentially more than 30 individual orphan diseases that we have historically all lumped together. As Dr. Haverkos was stating, there are likely subset-specific responses to various drugs that have been difficult to tease out in prior clinical trials, as this is relatively new and developing knowledge and because these previous trials were not adequately powered for these analyses.

Secondly, I would really like to emphasize, and I think it's been emphasized well, that patients with these diseases have very poor

outcomes. With a 5-year survival of about 30 to 40 percent for most subsets, it's a very deadly disease. Primary refractory disease is very common. We actually recently published data that, at least in some subsets of PTCL, CHOP-based front-line chemotherapy is no better than best supportive care with regards to overall survival, so it's quite revealing and I think very appropriate, in my opinion, that even in the front-line setting, clinical trial participation is the preferred treatment for the NCCN guidelines for these diseases.

For those that that do receive front-line chemotherapy, over 75 percent will relapse at some point, many of them with very aggressive disease within the first year of completing front-line chemotherapy, and in that setting, the median overall survival is about 6 months when using cytotoxic chemotherapy, and that's despite the relatively high reported response rates to cytotoxic chemotherapy. The issue is that those responses are very much lacking in durability. So

this highlights the very valid point made earlier this morning by Dr. Mehta regarding the lack of correlation at times between surrogate endpoints and overall survival. So given the poor outcomes with cytotoxic chemotherapy, not only in the front-line setting, but also in the relapsed setting, four novel agents have, at least at one time, been made available for use in this patient population with relapsed or refractory PTCL.

These agents have already been discussed, but I would like to emphasize a couple of points about these agents. Most importantly, that only two really functionally currently remain for use on the market currently. Both of them, belinostat and pralatrexate, are the subject of today's ODAC meeting. One drug, brentuximab, it's approved only in the relapsed setting for the ALCL subset; however, the role of this agent in the treatment of relapsed disease is unclear at this time since in the post ECHELON-2 era, the vast majority of patients should have received this agent in the front-line setting, and it's unclear if retreatment

in the relapsed setting with this agent will be beneficial. The other, romidepsin, as has already been discussed, had its marketing authorization removed after a failed confirmatory trial. So really, for this very deadly and chemo refractory disease, we're left with two drugs, pralatrexate and belinostat, which we're discussing today.

So there's been a lot of data presented regarding the efficacy of these agents. I'm not going to stand here and tell you that I believe that these are the answer to treatment for PTCL, the end-all and be-all. Clearly, they leave a lot to be desired with regards to response rates; however, I think it would be very safe to say that at least a subset of patients -- and some of that may be PTCL subtype-specific -- clearly a subset of patients benefit from these drugs. Compared to traditional cytotoxic chemotherapy, which would be the only alternative in the absence of these drugs, I think the most notable outcome to me is the reported duration of response that we can see with these agents --

DR. CHEN: I'm sorry --

DR. RENEAU: -- even though they may have a low response rate.

DR. CHEN: -- to interrupt, but you are running over time at this point. Could you please wrap up?

DR. RENEAU: Thank you.

So I think I'll just end by emphasizing that in my academic clinical practice, I have the luxury of having many clinical trials available for patients with relapsed PTCL; however, the vast majority of patients for various reasons are unable to participate in those. So even in my own academic clinical practice, I would find it very difficult to treat these patients in the absence of these drugs, and my worry is even greater on behalf of the many community oncologists that I collaborate with, who in the absence of these drugs would really be left with little to nothing to treat these patients with. Thank you for my time.

DR. CHEN: Thank you.

Moving on, speaker 8, please unmute and turn

on your webcam. Will you begin and introduce yourself? And please state your name and any organization you're representing for the record.

DR. MATHEW: Hello. My name is Reuben Mathew. I'm a resident physician and combined internal medicine and pediatrics in New Orleans, and I'm a member of the FDA Task Force for Doctors for America. I receive no funding from any pharmaceutical or medical device industries.

My patients routinely have very complex medical needs without the resources to combat them. As a practicing clinician often working up to 80 hours a week in the hospital or clinic, I have limited time to secure resources outside of what is readily available. These time constraints are not unique to residents, but also practicing physicians who have limited bandwidth to delve into the primary literature to determine if an FDA-approved treatment is safe and effective for their patient.

We rely heavily on the FDA in conducting a robust review process and awarding approval to drugs as the gold standard for safety and efficacy.

If the FDA approves something, I trust it; however, it concerns me that there continues to be a significant uncertainty for several treatments granted accelerated approval and their clinical benefit well after their initial approval due to delays in completion of the required postmarket studies. Manufacturers and being awarded accelerated approval are making a promise to the FDA, to clinicians like me, and my patients that they will in a timely manner provide evidence that the drugs granted early approval do indeed work as predicted. Not completing these studies in a timely manner burdens patients by prolonging uncertainty around unproven treatments.

My patients deserve treatments that are truly safe, that work, and that they can afford, and for every day that these drugs are on the market with incomplete data, they will be prescribed and cause potential medical and financial harm. Pralatrexate and belinostat are among some of the most delinquent and expensive products with the required postmarket studies, more

than doubling the 3 to 4 years goal of completion of oncologic studies.

Until the FDA can meaningfully enforce these requirements on postmarketing requirements, I'm worried that manufacturers will continue to de-prioritize and delay the necessary confirmatory trials. Simply put, only medications that are proven to work should be available. I ask that the FDA withdraw these two drugs from the market to protect patients at risk of continued clinical and financial harms, as well as to incentivize the manufacturers, if they truly believe these drugs are clinically and meaningfully effective, to complete their postmarketing studies. Accelerated approval is not traditional approval, and we support FDA's efforts to ensure that the promise of confirmed clinical benefit made by manufacturers when receiving accelerated approval is kept to these vulnerable patients. Thank you.

DR. CHEN: Thank you.

We will now move on to speaker number 9. Speaker 9, please unmute and turn on your webcam.

Will you begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. KROMMES: Good morning. My name is Janet Krommes, and I'm speaking to you about Folotyn, which is the brand name for pralatrexate. I am rather unique in the group of people who are speaking today. I'm a clinician. I have long-standing experience in rheumatology, but I have no specific expertise in studies or statistical analysis; however, I have devoted my career to helping people make the best treatment choices, and it is from that perspective that I'd like to address this today.

I do represent Doctors for America, I am on their FDA advisory committee, and I am employed by a private rheumatology practice. I have absolutely no connections with any pharmaceutical industries. I learned early in my career that a bad drug can do well with good marketing, and so I do not confer with pharmaceutical representatives in any shape or form.

I would like to point out that the landscape between 2009 and 2023 is vastly different. Pralatrexate is an analog of methotrexate, which is a drug which rheumatologists are well familiar. It's more potent, its intracellular concentration is at least 14 times that in methotrexate, and like methotrexate, it shows promise in the treatment of a spectrum of malignancies, but in 2009 was able to demonstrate a special class effect for end-stage PTCL. And on the basis of a study which was phase 2 and which included surrogate markers for potential efficacy, this drug was granted accelerated approval, and I think, as any clinician would state, when you have no options, any potential option is justifiable in use.

But 2023 has brought us a very different landscape. It's been 14 years without adequate data to support efficacy and safety of this drug; multiple novel agents have been approved in phase 2 studies; we now understand the impact of individual subtypes on both therapeutic options, as well as therapeutic responses; and there have been paradigm

shifts in the treatment of end-stage PTCL.

This slide is simply to introduce in a written form what has already been said by numerous speakers. There are limited drugs that are approved for end-stage PTCL, and I will point out that I do not think that the data on pralatrexate is outstanding in comparison to other agents, and that clearly more understanding is needed before we know how to use this drug. This slide does not contain other drugs which are currently under investigation and which also have encouraging early results.

A criticism of the PROpel study upon which accelerated approval was granted has been criticized because the rate was largely different by partial responders. We understand now, in a way that we didn't in 2009, how little clinical significance this particular response can have, and yet approval for this drug and use of this drug is based on those numbers. Further studies have not really added to our understanding. There have been small phase 2 datasets that are available that we

can evaluate, but to me as a clinician, the numbers look comparable, and we have no comparator data, no true safety data, and we still don't understand what the risks and benefits of this drug are in clinical practice; and yet, certainly this drug will be used without complete understanding.

The real-world efficacy is something that's very important to me. I was practicing in the late '80s and early '90s when zidovudine was approved, and like zidovudine, this drug has an astronomical cost, and in the real world, that has an impact on what we can prescribe and how we prescribe. And this small study from Korea demonstrates that real-world physicians, when faced with the astronomical costs and uncertain benefits, may make their own decisions in terms of how they use this drug. In this study, this resulted in a significant drop in the response rate, and yet the toxicity was similar to that seen in the PROpel study.

In terms of safety, as a rheumatologist with very deep use of methotrexate, albeit at low doses

where we have less toxicity, what struck me here was the metapneumonitis seen in this small PROpel study. In rheumatology, we know risk factors for pneumonitis with use of methotrexate; that is male gender and diabetes. In this setting, we have no idea what the risk factors are for the use of pralatrexate. Even more concerning is that postmarketing studies have shown severe dermatologic reactions, and these reactions can be idiosyncratic, they can occur after one dose --

DR. CHEN: Excuse me. We are running over time for your section. Can you please wrap up?

DR. KROMMES: -- I sure will -- and that could be fatal. And we could skip this slide because it doesn't help.

If I may skip to the conclusion, there is clearly an unmet need for treatment of end-stage PTCL, but there's been a change in standard of care, a change in our understanding, and to prescribe a drug without confirmatory studies, without understanding true risks and benefits, is to put patients in harm's way. And I would

strongly urge the FDA to withdraw consideration of this drug without confirmatory studies. Thank you so much for your time and attention.

Clarifying Questions (continued)

DR. CHEN: Thank you for the public comments. The open public hearing portion of this meeting has now concluded and we will no longer take further comments from the audience.

As we have additional time, we will now take remaining clarifying questions to the FDA and the sponsor. Please use the raise-hand icon to indicate that you have a question and remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. Please remember to put your hand down after you have asked your question.

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

move on to the next panel member.

I would like to begin the questioning with a comment to the sponsor. Given that PTCL is such a heterogeneous disease and the data that's been out there of HDAC inhibitors having preferential activity in AITL and T-follicular subtypes, as multiple speakers have noted, and the negative results of the romidepsin confirmatory study and unselected PTCL, would it not make more sense to restrict the belinostat eligibility?

MR. MINGMONGKOL: Sure. Let me turn this over to Dr. Iyer who can talk about the design of the trial.

Dr. Iyer?

DR. IYER: Thank you, Dr. Chen, for this question. It's a very important question, and we've learned a lot from the romi-CHOP randomized study. I think at least in the the phase 3 PMR, the key inclusion is only a few subtypes that will be included, including the PTCL not otherwise specified, and angioimmunoblastic T-cell, follicular helper phenotype, and others, including

extranodal NK T-cell. The leukemic and the cutaneous varieties are excluded.

In some ways, I think even though the Part 1 and Part 2 are designed -- Part 1 for dose optimization -- I think it's a good question for us to revisit at the time of the data that's available at the end of two years and perhaps make some of the subtypes more stringent based on the available data. Thank you.

MR. MINGMONGKOL: And --

DR. CHEN: Thank you. Sorry. Go on.

MR. MINGMONGKOL: Well, you also had mentioned romidepsin versus belinostat, and I just want to make sure that the committee understands the difference between the products. They are not the same even though they're both HDAC inhibitors, so Dr. O'Connor, if you could comment on that.

DR. O'CONNOR: Thank you. I actually want to comment more broadly on the observation about HDAC inhibitors and angioimmunoblastic T-cell lymphoma and the T follicular.

I think this data, which is suggestive, none

of it has been randomized. Much of it is small subset analysis and much of it is pooled, and there's a lot of variability. I think what the data suggest is that there's a modest benefit, and we need to explore other strategies in these particular subtypes. The HDAC inhibitors have been associated with small improvements in the progression-free survival in angioimmunoblastic and T follicular, but probably some of the best data, and yet another reason I believe these drugs have merit to stay around, is combinatorial epigenetic therapies producing really important overall responses and improvements in progression-free survival.

I think the ability to allow the field to continue various clinical research endeavors to explore how to combine these novel drugs, epigenetic predicated or not, I think affords yet another parallel strategy to be considered as we continue to try to define optimal treatments for not just that one subtype but all subtypes of PTCL.

DR. CHEN: Thank you, Dr. O'Connor.

Dr. Thanarajasingam?

DR. THANARAJASINGAM: Thank you so much. I am a clinician first, so I echo a lot of the comments that have been mentioned by my panel members and the speakers in the open public comment. There's no question we need more options to treat patients with this disease and that each option is meaningful, but also that the FDA bears this public health onus of confirming efficacy and guarding the safety, and the confirmatory trial needs to get done.

I have some concerns to direct at Acrotech about the feasibility and accrual of the recently initiated confirmatory trial, even with the extended timeline that's been proposed. Dr. O'Connor made a fair argument about the necessity of anthracyclines in front-line treatment, but I think there are still differences of thoughts about that, and I'm concerned that not all lymphoma clinicians, particularly colleagues I work with in the community, would be enthusiastic to put patients on a study without doxycycline in

one arm.

Additionally, there are studies that suggest an uncertain relationship between CD30 expression and the benefit of BV-CHP, the ECHELON-2 regimen. I think we're seeing more use of BV-CHP in front-line patients with any level of CD30 expression, whether that's right or not as a separate discussion. CD30 expression varies across PTCL, but a fair estimate is 30 to 50 percent, so clinicians may not accrue those patients on this trial.

So I think there are legitimate concerns about the feasibility, and even if we get this done and the front-line study is negative, I will still wonder is there a role as a single-agent therapy, as many of my colleagues have mentioned, for some PTCL patients or some specific PTCL histologies in the relapsed/refractory setting. And to give these agents their best chance, can we hedge our bets and also complete a smaller study in relapsed/refractory PTCL that would be something that we could design to be attractive to patients

and clinicians for enrollment with a dose-finding component and a part 2 with a PFS endpoint? This would give an opportunity to define the optimal dose in the relapsed/refractory population and also complete an additional confirmatory study in the population where you can get a quicker readout on survival endpoints.

Just one last comment that hopefully the FDA can comment on just in terms of actionability and what happened from here, I am concerned that we cannot come back in two years and show that we achieved the dose optimization study portion with the 75 patients. Then the major concern is will the full study results even be available in 2030. We don't want to be in the same situation in 2030, so around that time frame, with the FDA's substantial involvement, I think the drug development plan would have to be reevaluated.

So I'd love to give Acrotech a chance, and I appreciate the insights of the disease experts on that team on my comments about the feasibility and accrual challenges and for the FDA to talk about

next steps in the future. Thank you.

MR. MINGMONGKOL: Sure. I think you made some suggestions, and I think there's a separate discussion on the suggestions that you have done to speed up the timeline. But the heart of the question that you've asked is really about our ability to recruit and our ability to meet these timelines, so what I'd love to do is invite Dr. Anvekar who can talk about the things that we have in place to address timely completion of these trials.

Dr. Anvekar?

MR. ANVEKAR: There are two aspects to the question. One is, like you rightly pointed out, the Folotyn plus the COP arm. So what I would like to say is that the protocol has been submitted to all the sites as we mentioned, and 77 sites to date have agreed to participate in the study. That is what gives us the confidence; that they have reviewed the protocol, the protocol has been approved by the IRB, and currently it is also being reviewed at the local country levels and their

individual requirements, as may be. So that is one aspect which gives us the comfort level that the protocol has been reviewed and may not be the most rate limiting factor as of now.

Second, at the end of Part 1, we will know how the data is reading out to make a more informed decision about Part 2. All these data will be reviewed along with the FDA to make the best judgment on how we can proceed to the next step. Also as the FDA mentioned, we will also want to keep them updated on the progress of the study so that we are not into three years down the line, and then we are in the same state.

So we agree that we should also be giving the FDA progress updates on a more frequent basis so that we are tracking towards -- and if we are not tracking for any reason, then at least have an open conversation with them to say why it is not happening. But the specific scientific aspect of the FOL-COP, maybe I can ask Dr. Iyer to comment in terms of from a science perspective more. I'm just speaking more from a recruitment and the trial

completion part of it.

DR. IYER: Thank you for the question, Dr. Thanarajasingam. This is Swami Iyer from MD Anderson. The landscape of treatment is changing in PTCL, and hopefully we'll have other therapies, and that's everyone's wish and hope as we treat patients with lymphoma. And you're right; at least the brentuximab that you alluded to and its applicability has to be confirmed in a study. There is an ongoing study.

Will that change potentially in the U.S.? Yes, but I think the benefit here also goes beyond the U.S. and other countries where we don't have a front line approved for brentuximab. I think one of the ways the study is designed, as an investigator and as you look into the heterogeneity, is at least we have two parts, and the first part will help us inform how we will proceed with Part 2. You're absolutely right, and in some ways this, the partition, helps us to think through this very complex process, and hopefully in two years, as we think through this, we will have

better answers for our patients. And who knows? The landscape could change, and for most drug approvals that are still waiting to be approved in the relapsed/refractory setting, I think that's probably a longer timeline as well. So we want to make sure that our patients are treated and get the best possible outcomes. Thank you once again.

DR. RICHARDSON: Hi. This is Nicholas Richardson from the FDA. Is it ok to respond from our side?

DR. CHEN: Yes, please.

DR. RICHARDSON: Hi. So thank you for the question. I think it goes back to some really important points. We've learned a lot from the accelerated approval program from our experience. Part of your question really goes to accrual and making sure we have an updated status on that accrual rate.

One component of that, that we had mentioned and that we continue to work with the sponsor on, is also the number of sites that are being activated and where those sites are located. I

think it was mentioned, for PTCL, there is an importance to ensure that there is a representative population, as there's a lot of heterogeneity that's been talked about quite a bit today. So in addition to that accrual, I think having a transparent status update on site activation and where those sites are located will really help meet those goals of assessing feasibility and the status of that trial at that time.

From a regulatory perspective, as mentioned, we do work with the sponsors to create milestones as far as trial completion date and when the results will be available. So those are milestones that are agreed upon between the sponsor and the FDA, and those milestones are important aspects as we think about the accelerated approval program and the timely verification of clinical benefit.

Then just the last comment is related to conduct of a trial in the relapsed/refractory setting. We often encourage sponsors to have a comprehensive development program, as Dr. Mehta mentioned, and that can include trials in different

treatment settings. So because of the limited treatments available in the relapsed/refractory setting, that is one thing that could be further explored here, and the FDA would encourage that because at the end of the day, we do want to move the field forward. We do want to have safe and effective therapies for patients.

DR. PAZDUR: Could I just jump in here? I want to second that point and would like to have this company discuss this. The development of this drug, let's face it, is, for lack of a better word -- not to be overcritical -- just say suboptimal, and I'm being kind by using suboptimal rather than other words here. I don't want to be back, as you pointed out, years later with a negative trial and be in the same situation.

Could the company address -- because this drug has not been developed well -- having a more robust program for the determination of clinical benefit; in other words, do two clinical trials, and the second one being in the relapsed/refractory population? And it could be a very simple trial.

It could be their drug -- or their drugs, plural -- against dealer's choice, so to speak, whatever the physician would choose. We've seen that multiple times in solid tumors, for example, where there are very little effective therapies. And this would not be a competing protocol to the first-line study but would also be there if we have problems and also lead to the confirmation of benefit perhaps even more rapidly than a first-line setting.

So what is the company's opinion on this? I'd like to have a discussion on this. I think it's one that is something that I'd like to hear a commitment from the company on this, really, because here again, no one could say that this drug was developed with due diligence. No one with a straight face could say this drug was developed with due diligence. So we're really in a situation where patients are caught in the middle here, and I feel very bad for that situation and very bad for the patients that they don't have this information, and I really think it's up to the company to step

up and really develop this drug, and make sure that we're not here at the year 2028, 2030, 2031, having this discussion.

So could the company address this issue?

MR. MINGMONGKOL: Dr. Pazdur, is your question around doing two trials --

DR. PAZDUR: I'll make it quite clear. Are you committed to developing the drug in a relapsed/refractory setting to address this issue, to give us more confidence in this drug with a shorter timeline?

MR. MINGMONGKOL: Sure. Let me turn that over to our president, Dr. Anvekar.

MR. ANVEKAR: So as of now, at this very stage, I would say we are just looking into it. We have looked at relapsed/refractory. When we have had the discussions on the possibility of the accrual of this trial with the experts in the field, often we have been told, "Look, we know the drug works, and how do I do a clinical trial in the same indication where I know the drug works?" That has been posed as a challenge, but what I would say

is if there is a possibility of looking at it, we will certainly want to complete this because I think that could be a shorter path.

DR. PAZDUR: Well, I'm talking about doing both trials, not just the relapsed/refractory drugs, obviously. Right.

MR. ANVEKAR: Yes, doing both trials at the same time could be an option, but it's just a little bit difficult for me, as you can appreciate, to make a commitment at this stage without having looked at the whole feasibility.

DR. PAZDUR: Well, I urge you to circle back to the FDA on this topic in an expeditious manner, so to speak, because I think it is one here that the development of this drug is suboptimal. And I realize it's not entirely your responsibility, you inherited some of these problems, but it really needs to be addressed. And here again, I don't want to be here -- hopefully -- in the year 2035, or whatever, talking about the same problem.

As I pointed out, there are many reasons a clinical trial can be negative, this randomized

trial -- underpowered, not looking at the correct subgroup -- and for us to be back at the situation. We really need more information on this drug. And here again, because of the inadequacy of the development program here, over the the 10-plus years here, we really have to step up to the plate here. And I think that's what you've been hearing, even in the open public hearing. You have a responsibility to do this, and we'll hold you to that responsibility.

MR. ANVEKAR: Yes, absolutely. Yes. On the relapsed/refractory setting, we will come back; absolutely.

DR. CHEN: Thank you for those comments and we'd like to move on. And I would remind the panel members to try to please focus their questions so that we can get to as many panelists as possible, and please remember to state your name before you speak.

Dr. Rosko?

DR. ROSKO: Ashley Rosko, Ohio State. My question is around strategies to promote timely

completion, which my question is about accrual and ways to be able to enhance accrual to allow for timely completion. My question is both to the applicant and to the FDA. One of the ways to be able to enhance accrual is to be able to devise eligibility criteria that are not overly restrictive in the phase 3, randomized-controlled trial settings.

Can the applicant comment on whether or not, from the early-phase clinical trials to their later phase clinical trials, if the eligibility criteria have been expanded? And then can the FDA weigh in on the guidance that provides for industry regarding eligibility trials and whether or not they can be more expansive, and how the FDA is able to enforce more liberalized eligibility criteria for phase 3 randomized trials?

MR. MINGMONGKOL: Would you like for the sponsor or FDA to go first?

DR. CHEN: Sponsor, please go ahead.

MR. MINGMONGKOL: Okay. I'll invite Dr. Anvekar, who can talk about the eligibility

criteria, as well as our recruitment strategy.

Dr. Anvekar?

MR. ANVEKAR: So for the Part 1 of the study, the inclusion and exclusion criteria have been modeled around the romidepsin plus CHOP, so we believe that this gives us a broad enough patient category so that the enrollment can happen in the timeline, which we are projecting -- or in other words, the entry, the inclusion or exclusion criteria should not affect the patient population, and therefore any effect on the recruitment.

For the second part of the study, which talks about how the study is going to be conducted, as I understood your question correctly, we are going to implement many strategies, namely digital amplification if you would call it, to make sure that wherever the patient is identified, even in a geographical area surrounding the site, we can identify them and channel the patients to the site.

So like those, there are many other activities which we are discussing with our CRO. . The other option which we talked about was also the

sites who have mentioned that they do not have the resources right now to implement the trial, we are going to be working with them, and we have said we could provide them the resources if that is what the bottleneck. So we are working on various aspects to see how we can best get through the enrollment targets, and I think our first and foremost startup was just identifying the sites and the countries where we have the maximum possibility of accruing the patients.

DR. CHEN: Thank you.

FDA, do you have any additional comment?

DR. RICHARDSON: Hi. Nicholas Richardson, FDA. Just quickly, from an eligibility standpoint, you raise an important consideration, and here at the FDA we do encourage broad eligibility. There has been a paradigm where the clinical trial population may be different than the population for which the drug is actually administered following approval, so any ability to narrow that gap would be a benefit to patients. So broad eligibility is something that we are open to and encourage

sponsors to consider as well.

Then as far as conduct of the trial, for this trial I think there are specific things that that we can talk about, but from a looking-forward standpoint, I think this is really where the paradigm of having confirmatory trials well underway at the time of accelerated approval is ideal. As in Dr. Mehta's presentation, the difference between trials that verify clinical benefit that were underway at the time of accelerated approval was approximately 3 years versus those that had not yet been initiated. The time to verification or withdrawal was 7 years, and that's a long period of time of vulnerability for patients. So from a looking-forward standpoint, I think that's an important concept to take forward.

DR. ROSKO: Thank you. That is all.

DR. CHEN: Thank you.

Dr. Conaway?

DR. CONAWAY: Yes. Mark Conaway, University of Virginia. I have two quick questions, one for the sponsor and one for FDA. For the sponsor, the

phase 1 portion, you plan to enroll 15 participants in each of five groups in a highly heterogeneous disease. Are there plans for the possibility that the phase 1 trial won't result in a clear dose recommendation? And if so, how does that affect the overall timeline?

MR. MINGMONGKOL: Dr. Iyer, would you care to comment on that?

DR. IYER: Thank you for the question. At the part for the Optimus guidance, the trial does not have to be powered to demonstrate statistical superiority for the dosage, but the most important thing here is the dose optimization. There are various aspects, and I think the IDMC that's been tasked with looking at the totality of the data, particularly the safety, efficacy, the balance, and will convene. And once the significant patients are enrolled and once we have the analysis and primary endpoint of ORR at 3 months, the recommendations will be based not just on the overall response rate but also the other endpoints.

More importantly, there's a futility measure

here in place with [indiscernible], and that's the 20 percent or above. In other words, there are many multifactorial issues here that need to be taken into consideration as we move forward with the right dose for Part 2. It's quite possible that we might not see much difference from the ORR response rate, but the more important aspect here is looking at the safety. Thank you.

DR. CONAWAY: Thank you.

And a question for the FDA, I think I heard the answer to this earlier, but I wanted to ask very directly. FDORA gives the FDA the ability to set milestones, and I was wondering how broad that is. Can you set milestones based on safety and efficacy or interim analyses, in addition to accruals?

DR. MEHTA: Thank you for that question. This is Gautam Mehta, FDA. We had the ability to set milestones prior to FDORA, so typically with the accelerated approval, we'll set a milestone for the date the protocol is submitted, the final protocol; the date the study is completed; and then

the date that the trial results are submitted to us, so final report submission.

FDORA doesn't necessarily provide for additional milestones in addition to those three, but it allows us to, one, require that, prospectively, the confirmatory trial is underway at the time we grant accelerated approval, so in that case, that initial milestone of protocol submission has already passed because they've got the study underway, and then it requires just status updates. So every 6 months we're going to get a status update, and this is just rolling out, so this will hopefully engender more bilateral communication between the sponsors and FDA.

DR. CONAWAY: Okay. Thank you.

DR. CHEN: Thank you.

Dr. Nieva?

DR. NIEVA: Thank you. My question is for the FDA hematology team. It strikes me as being very strange that when a drug is behind on its development, the solution seems to be to promote the longest, most ambitious, most difficult

clinical trial that's ever been done in the disease. It seems like a much shorter trial would be appropriate to try to look at the endpoints, and I'm wondering if some other incentives could be made to do that.

Specifically, I'd like to have a sense of do we really need a second- and a third-line drug in this disease approved. Would it make sense to lift one of the approvals, recognizing that the T-cell lymphoma patients still have a second-line therapy option available after combination chemotherapy, and that relatively few patients go on to third-line therapy? Do we have any data to get a sense of how big of a population actually needs both of these agents and not just one of them?

DR. RICHARDSON: Hi. Nicholas Richardson, FDA. Thank you for your question. I think maybe you had two questions and I'll try to clarify them. One was you had asked about could we look at endpoints regarding this confirmatory trial and the verification of clinical benefit, and then also the number of treatments that are being evaluated

within this trial.

Is that a fair representation?

DR. NIEVA: I'd say the first part of the question is really getting back towards Dr. Pazdur's point that, really, a less ambitious clinical trial maybe would be appropriate so that we get a faster answer; not a 7-year answer but a 2- or 3-year answer. Now that the company is committed to enrolling 100 patients a year on a subsequent trial and appears to have the resources to do that, is there a 100- to 200-patient study that could confirm clinical benefit, or should the agency even think about telling the company, "No, you need to have a 2-year trial here, not a 7-year trial?"

DR. RICHARDSON: Sure. Thank you for clarifying that. As we mentioned, overall for accelerated approval, the expectation is that these confirmatory trials are completed in a timely manner. Obviously, that's not the situation that we're dealing with today. So to address your question, really, the onus is on the sponsor to

provide data to the FDA to support that there is verification of clinical benefit. Yes, we do work with the sponsors on the development of these confirmatory trials, but it's the sponsor's responsibility to conduct and design these trials for verification of clinical benefit.

Now, as part of the reasons that we wanted to hold this meeting today, we want to be transparent about some of these outliers for accelerated approval, and you raise an important point. So there is a collaborative discussion to inform whether a timely clinical confirmatory trial can be completed; however, for this situation, we're in the situation that we're in, and the sponsor has elected to choose this randomized trial in the first-line setting. We have been open to trials in multiple disease settings like we had mentioned, but at the end of the day, it's the sponsor's responsibility to conduct these trials.

DR. PAZDUR: That being said, if I could just weigh in here. This drug is not being developed, obviously, in a vacuum, and we have two

other trials that were done and completed, so the trial can be completed, and we know that because of the brentuximab and the romidepsin experience, and it did take several years, obviously 5 years plus, for the brentuximab and 7 years for the romidepsin.

We have to treat sponsors equally, so to speak, and if we were demanding randomized trials for these two drugs, why should we then say, "Well, you could do less here?" This is why I'm advocating that they do an additional trial in addition to this front-line setting.

Your comment regarding taking one of these drugs off, that is like, which one would you take off? Why would you choose one drug over the other? That puts us in a very precarious position, so to speak. If this was two sponsors basically having two different drugs here, how would you choose one sponsor versus the other sponsor? It puts us in, really, a very difficult -- legal even -- paradigm of doing that, saying, "Well, we're taking one drug off and leaving one drug on." So there are issues that are regulatory and also legal that comes into

play when one starts removing drugs from the market.

DR. CONAWAY: Well, I would point out that you could choose the one that's got the longer delay.

DR. PAZDUR: Thank you.

DR. CHEN: Thank you for the comments. We are running short on time, so I would ask people to please just ask one focused question.

Dr. [Mr. - sic] Mitchell?

MR. MITCHELL: I'm not a doctor. I am the consumer representative to the ODAC and I also have the experience of benefiting from accelerated approval. Three of the four drugs that I take right now for my multiple myeloma were approved through accelerated approval, so I'm a big fan.

I want to not ask a question partly because Dr. Pazdur's asked specifically at times if we can discuss and reflect as a committee, and I want to talk about discussion question number 1, which asks whether the current plan to verify clinical benefit is reasonable, considering the proposed timelines.

And in regard to that, I would like --

DR. CHEN: Excuse me. We actually have a session right after this to go on to discuss the questions to the committee, so I would like to defer your comment to that section.

MR. MITCHELL: Well, it's linked together in the agenda.

DR. CHEN: Yes, that's right.

MR. MITCHELL: It says questions to the committee and discussion at 12:45. I thought we were here.

DR. CHEN: Sorry, but we're still finishing the questions to the sponsor and FDA right now that we had to cut short earlier, and we will certainly circle around back to you when we open up to the general committee discussion questions. I'm sorry for the mix-up.

Dr. Spratt?

DR. SPRATT: Dan Spratt, UH Seidman, Case Western Reserve. This is to the sponsor. Other than, obviously, keeping this approved, there is financial incentive to keep this until let's say

this reports out in 2030, whether positive or negative, so another, we'll say, 6 years on the market. I guess the question, though, in terms of actually focusing on the patient and benefit, if these both were removed from being approved, you effectively would not have any contamination or it'd be much more challenging in this proposed randomized trial, where there's basically no FDA-approved or effective therapies in the relapsed/refractory setting, assuming first-line therapies are being used.

So why is it not in the trial's interest and the company's interest, other than the next 6 years of financial gain, to not have these withdrawn so that your first-line, large trial, if these are active agents, you would see a larger effect size if there's no salvage use of these for impact on survival?

MR. MINGMONGKOL: Let me turn this over to Dr. O'Connor. I would like him to emphasize the need for both of these products without a gap.

Dr. O'Connor?

DR. O'CONNOR: Yes. Thank you for this interesting question. I guess the first is the precedent, and the precedent is that it's not uncommon in these scenarios that the approved drug stays on during the period of conduct of the clinical trial, but I'm going to answer the question more from the perspective of the patient.

It was noted earlier that there are two FDA-approved drugs -- and maybe we can take one off; we only need one -- and I would argue that there are two FDA-approved drugs. Take one off, we have one. The answer is that many patients are receiving both drugs, and by virtue of the fact that these drugs work in different ways with different toxicity profiles, it's likely, in fact common, that patients are benefiting from both of these drugs.

So in in terms of thinking about comparisons to chemotherapy, there are a number of registry data that we alluded to that suggest that these new drugs are looking better than what we see with conventional chemotherapy. And I'm going to share

one data from Dr. Foss' study and one from a study we did, and these are retrospective with all the acknowledged limitations of these kinds of registry studies, but this is the data we have at hand.

These data clearly suggest that the newer drugs provide advantage over the historical ones. In addition, some of these registries have explored the issues of toxicity of these new agents in comparison to conventional chemotherapy, and I'm going to put this slide up now just for a quick comparison.

It's also clear that the combination of chemotherapy in this setting is wrought with all sorts of toxicities, so I completely appreciate the issues about the toxicity of these agents, but you need to couch that in the context of what's the toxicity these patients will receive with the conventional combination chemotherapy. And again, retrospective registry data, single-agent data on the right, combination on the left, it's very clear that there may be both clinical benefit of these drugs, as well as a toxicity benefit that favors

the single agents, and it's intuitive that single agents will be less toxic than combination.

So I personally would advocate strongly for maintaining both of these drugs to be available for all our patients with PTCL, irrespective of the line of relapse.

DR. SPRATT: To restate the question I guess very clearly, by keeping these agents approved, they will be used in the second-line setting. How is that going to, if anything, help the positivity of this trial, especially for the important endpoint of overall survival?

MR. MINGMONGKOL: Dr. O'Connor?

DR. O'CONNOR: It's clear that that could be a confounding factor, and that statistical conundrum needs to be weighted against the benefit of using these drugs for patients, where there is no other option to treat the disease.

DR. CHEN: Thank you.

DR. SPRATT: Just real quick. If that becomes negative, let's say contamination, and ultimately the drug does not get approved in 2030

because of this contamination, then is there really then a net benefit? So I guess that's just a comment, but thank you very much for your response.

Questions to the Committee and Discussion

DR. CHEN: Thank you.

In the interest of time, we will now turn our attention to 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 public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. After I read each question, we will pause for any questions or comments considering its wording. We will proceed with our first question, which is a discussion question.

Question 1. Discuss the delays in post-approval confirmatory trials for pralatrexate and belinostat, and whether the current plan to verify the clinical benefit of these products in

patients with peripheral T-cell lymphoma is responsible [sic - reasonable] considering the sponsor's proposed timelines.

The question is open for discussion.

Dr. Spratt?

DR. SPRATT: You want to have David Mitchell go first, just because he was going to speak last time?

DR. CHEN: Sure.

Yes. Dr. -- sorry. Mr. Mitchell, would you like to speak?

MR. MITCHELL: You keep promoting me. I'm ok with that, but I'm not a doctor. And thank you, Dr. Spratt, for that. That's very kind.

I want to ask to have the FDA slide number 61 pulled up, if I can. I'd like to speak to that, and then slide 68 from the FDA. Is that possible; 61 first? So directly going to the question -- can we get the slide back for me? That would be helpful; 61.

The timeline proposed, is the plan reasonable? When I look at this slide, and I think

about the degree and duration of uncertainty that we are putting on patients -- Dr. Pazdur talked about the development process being suboptimal -- I know that the sponsor isn't responsible because of the transfer of ownership for all of this, but this is a truly remarkable extension of what is intended under the accelerated approval process, which is for patients, and it needs to protect patients and keep that period of uncertainty within a reasonable amount of time. And I would say we are beyond a reasonable amount of time, by any measure, given the intention and general parameters that are used for accelerated approval.

So this poses a real problem, and it's exacerbated by slide number 68, please. You know, looking at this as a patient -- I think it's 68; for a second, if we can pull that up, and this has to do with the dosing levels. The idea that we are using -- we really have no dose optimization. I am a patient who has benefited from dose reduction and research showing that a lower dose was just as effective as a higher dose, and I believe one

representative of the FDA said that higher exposure to the drug didn't improve outcomes.

So here we are looking at a slide where the dose was being pushed as hard as possible. I heard someone mention higher doses were tested in other studies. So when I think about the period of uncertainty we've subjected patients to, the uncertainty regarding the dose, the fact that the drug doesn't necessarily work and may make their lives worse, it's very troubling, and it feels like we're trying to rationalize this plan, which extends this time out to potentially 2030.

So my answer -- I got to go back to the questions; forgive me, I've got too many mouses going and too many computers -- is that it is not reasonable. The current plan to verify clinical benefit is not reasonable given the proposed timelines and the risks to which we are subjecting patients, and potentially causing harm.

DR. CHEN: Thank you for those comments.

Could you please show discussion question 1 again? I just wanted to make sure that people feel

this question is clear and they have no concerns about the wording of this question.

(No response.)

DR. CHEN: Alright. We'll move forward then with further discussion of this question.

Dr. Spratt?

DR. SPRATT: Thank you. Dan Spratt, UH Seidman, Case Western. I would echo I'm on the fence, that this probably is not reasonable. But if you were able to just show slide 17 from the FDA slide deck presentation, given really how far of an outlier this really is in terms of time here.

Just to keep things in perspective, so while, yes, the onus is on the sponsor to have resolved this, I would also say, very respectfully, the onus is also on the FDA that we're now at this point right now, and should we be at this point. It's probably why we're having this meeting today. I will also say that I am very concerned that if we just take the premise that these drugs work for a moment and that these drugs benefit patients, then getting these drugs a traditional approval would be

in patients and, obviously, the company's best interest.

The most probable way to show that there is objective response rates, progression-free survival response rates, and even signal, if not OS benefits, is if these are not, if the approval is either withdrawn or removed, this accelerated approval, that there is not necessarily access to these agents off trial, so I am still perplexed by keeping them approved for 6 years.

The third point I guess is I go back to this surrogacy aspect. For a traditional approval, there needs to be some demonstrable benefit and outcome for a surrogate to be improved. And we keep going back to this; that these endpoints are not surrogate endpoints, and I do believe there is data that can be used to establish a surrogate threshold effect. If you look at the response rate in brentuximab versus these agents, can you, in a quicker, potentially even smaller trial, establish a higher bar of what is necessary to hit as an objective response rate?

My concern is that the big reasons that they say this has not reached the traditional approval to date and the trial was not done were -- I counted -- six points, and I'll say them fast. One, this is an aggressive disease. Plenty of drugs are approved in aggressive disease.

Rarity of disease; plenty of drugs are approved in rare diseases with trials, and this is a high event rate. Issues with standard of care, and they kept saying CHOP didn't undergo randomized trials. One of the public speaker's comments said there may not even be activity or benefit of CHOP versus best supportive care. So again, that doesn't help the argument that we're just using agents to these patients that have toxicity that don't necessarily help them.

That there are no other approved therapies; again, if romidepsin was the only therapy in this setting approved, should we be giving it right now, given that it nearly doubled the grade 4 treatment-related adverse events? Biologic activity; they've shown romidepsin's a great

example, but across all of oncology, many drugs have response rates that do not translate into quality- or quantity-of-life benefits. The biggest factor that remains is they keep saying how heterogeneous this disease is, but we're still just proceeding forward with a trial, keeping all the heterogeneity in there.

So I really feel that some type of understanding of this disease, or maybe including it across other disease entities with similar mechanisms of response, would be beneficial. So those are my comments. Thank you.

DR. CHEN: Thank you.

Dr. Choueiri, you weren't able to ask in the previous session. Would you like to go?

DR. CHOUEIRI: Yes. Thank you very much. Toni Choueiri, Dana-Farber, Boston. I have just one comment and I have one question for the sponsor. I would like you to keep this slide. I think, overall, just based on slide 17, that set a dangerous precedent for the other sponsors and drug companies to have such outliers from the same

company. I think, overall, Dr. Pazdur was quite kind in mentioning the word "suboptimal" in the development. I would be just maybe one level less kind, and I would say the development of this drug has been sloppy, and that is being somewhat a bit kind. There has been perhaps many justifications why, but slide 17 will tell you that no matter what, there could have been at least one randomized study.

Now, the question is, will it benefit -- because that drug, I have personally no doubt, and that's my own assessment, based on the literature -- a subgroup of patients that today we cannot for sure identify? I don't know. Twenty percent? Would that 20 percent carry the whole trial, randomized trial, toward the survivor or a PFS benefit? I'm not sure.

I would urge the sponsor to start screening patients soon, open the study, and monitor every month's accrual. There are datasets now. This is not new. You can get as close to the target accrual as possible per month, and if not possible

for whatever reason, communicate directly with the FDA why. There has been 13 plus 9 -- 22 years cumulative -- delay in doing the studies. Again, that set a dangerous precedent that we don't like other sponsors to do; therefore, I would urge you to accrue to this study at any price and not continue with the same trend. At this point, I am not sure accrual will happen. I'm not confident, just because it has been 13 years only. Thank you very much.

DR. CHEN: Thank you. We will actually defer having the company respond, as this is supposed to be the intra-panel discussion at this point.

We are running very short on time. I would like to move to the question 2 discussion. Discuss strategies to promote timely completion of the confirmatory trial for pralatrexate and belinostat, and insights from this experience that may facilitate completion of confirmatory trials for future accelerated approvals.

Does anyone have any concerns about the

wording of this question?

(No response.)

DR. CHEN: Okay. We will go ahead with discussion at this point.

Dr. Lieu?

DR. LIEU: Thanks so much. I'll try to keep my comments relatively short. I'll just answer both questions in my comments. I agree with everything that's been said so far. I do understand that there are extenuating circumstances that greatly lengthen this process, some of which are outside of the sponsor's control. I do believe that the clinical benefit of these agents is still more likely present than not, and I feel like the presentations and the comments from experts in the field are really compelling.

We don't want to prevent patients from receiving active therapies that can help them, but we have to have that confirmatory study, and now, actually hearing the comments from the experts in the field, I actually have significant concerns about the feasibility of the confirmatory study,

and I agree with the comments that have been made, that I would strongly recommend a faster study in the refractory setting to avoid potentially harming patients for an additional 7 years, and that's assuming even that the proposed timelines within the confirmatory studies are met.

I understand with the new regulations in the future, the FDA can require confirmatory studies to be initiated. In this case, I think they actually should require this to be the case, as well as show an acceptable accrual rate. If the FDA and the sponsor do agree to move forward with the proposed confirmatory study, I think failure to meet certain milestones really should lead to pulling the approval for these agents. Just in general, I think serious consideration, given this extraordinary situation, should be given to providing a hard timeline as is instituted in other countries. Thank you. That's the end of my comments.

DR. CHEN: Thank you.

Dr. Nieva.

DR. NIEVA: Thank you. I'm concerned that the duration of the trial may be a business strategy to sort of run out the clock on the patents for these drugs, and I'm concerned that making the trial as long as possible is somewhat in the economic interest of the company. And because of that, it's not going to get any easier to have a hard timeline or pull these indications after the study has accrued 100 patients or 200 patients. I'm also concerned about the company being able to make decisions such as dropping one of the arms as one of these drugs gets closer to its patent expiration.

So my proposal here would be to ask the company to make these drugs available to the cooperative groups and have cooperative groups actually run a second confirmatory trial. This would allow us to have extra data, and of course would save the patient population the risk that this trial ends up being closed for lack of feasibility, and we all have an opportunity to continue to learn about these agents. Thank you.

DR. CHEN: Thank you.

Dr. Cheng?

DR. CHENG: Hi. Jon Cheng, industry rep. I just want to thank the FDA for bringing this issue forward. I think we all are in agreement that the learnings from this example is important as to how to move this area of accelerated approval, which I find to be very valuable for patients to have the majority of accelerated approvals confirmed to have that early access, and I think very valuable with the balance of this uncertainty period.

Now, I also want to appreciate the sponsor because many of these things that they're taking on currently, I find to be in good faith. My question is actually to the FDA a little bit. What can we learn and what are the strategies to promote it? I do think a lot of the concerns are a resource allocation decision. So my question to the FDA is, actually, have you looked at some of the delays? No one wants a very prolonged delay. But is it different between smaller companies and bigger companies, and is there a difference between rare

diseases and common diseases?

I would imagine a common disease from a company that has significant resources would be able to expedite a lot of these kind of delays in confirmatory trials or run multiple trials; however, I can also imagine in a smaller company with limited resources, with a burn rate, they have more challenges initiating multiple trials or multiple investigations. For example, refractory and relapsed, those are not easy trials to do when the accelerated approval is already there. You often have to go outside the U.S. or things like that, so there are challenges either way. But I do wonder if we can identify the causes of these prolonged delays and if there's a difference in the data between small companies, big companies, and then rare diseases versus common diseases.

DR. THEORET: This is Marc Theoret, FDA. I just wanted to start off, and I'll turn it over to my colleagues. One of the biggest issues we have seen in terms of delays is the presence of an ongoing trial at the time of accelerated approval

versus not having a confirmatory trial ongoing. And we heard, I just want to emphasize, 3 years median versus 7 years, so that is a big predictor of that.

Second is, whether it's a small company or a large company, that period of vulnerability for the patient is the same in terms of having a confirmatory trial either confirming the clinical benefit or demonstrating that the clinical benefit was not verified and drug comes off the market; so that's irrespective of the size of the company.

I just wanted to say in terms of this consideration of timelines and the authorities, FDA always had the authority for withdrawal of the approval based on this concept of due diligence, and with FDORA, there is now agreed-upon timelines for completion, as well as the benchmarks that we get there that could be considered in this due diligence assessment. But that period of vulnerability for the patient -- this is a patient-centric program -- is the same irrespective of company size, and I'll turn it over to

Dr. Pazdur.

DR. PAZDUR: Your question, small companies versus big companies, oh yeah, there's a difference, and my experience, the larger companies that are adequately capitalized to do these trials, and are doing them, come to talk to us much earlier. They do not have this philosophy of let's just do a small trial, get it approved first, and then sell the drug. There's a greater commitment there. And here again, I'm making a generalization here, and there are exceptions to everything I say here but, in general, larger companies have the adequate capitalization, the financial means, to do these trials.

What we saw, for example, with the PD-1 drugs -- and here again, I refer people back to that ODAC, the 3-day ODAC that we did -- not only was there one confirmatory study; there were multiple confirmatory studies in the same disease. What we see sometimes with small companies in our internal discussion is they say, "Oh, we don't have the capital to do a randomized study. We need to

get this drug approved, and then we'll capitalize this larger trial." That's unacceptable, and that's why we really are moving toward that these trials have to be ongoing at the time of the approval, with substantial accrual to it.

But we can't play this game of financial risk, and then putting that financial risk back on the patients. That's totally unacceptable, and that's why the FDA really was 100 percent behind this issue of these confirmatory trials being ongoing, substantially ongoing, at the time of the accelerated approval, but there are differences, again, generalization, and there are always exceptions to the rule.

DR. CHENG: But if I may, I think the requirement for the initiation or accrual of the confirmatory trial will help tremendously to your data and will help both small and large companies --

(Crosstalk.)

DR. CHEN: Excuse me. This is supposed to be the intra-panel discussion part, so if we will

please move on at this point rather than questions directed to the FDA or the company.

DR. CHENG: Thank you.

DR. CHEN: Sorry about that.

DR. CHENG: No. Thank you.

DR. CHEN: Dr. Advani, you weren't able to ask your question during the prior session, so would you like to go now?

DR. ADVANI: I think the issue is with taking the drug, which has been shown to be effective, at least which some of us have used in the relapsed setting, and now trying to prove the efficacy in front line and the challenges associated with it. We do need it in the second-line space because otherwise there's nothing to bridge these patients to, even an allo transplant.

Is there a way the front-line design can be modified that you have a very stringent interim futility analysis for efficacy or toxicity, which forces the question earlier rather than waiting 7 years?

DR. CHEN: Do you have a suggestion about that? We're not really having the responses from the company and the FDA at this point.

DR. ADVANI: Well, in a [indiscernible], how can you make the timelines shorter.

DR. CHEN: Do other panel members have thoughts on that?

DR. SPRATT: Yes. Are you opening up to any of us?

DR. CHEN: Sure. Dr. Spratt?

DR. SPRATT: Yes. I think Dr. Nieva had a great suggestion, and I do think that's a balanced fair assessment given, to pick one of these agents, A, to focus in on it, and B, to better understand, even in this sort of phase 1 portion, enriching -- I mean, we're just throwing darts blindly, I feel like, in a heterogeneous disease, so rather than solely trying to find dose, I think we also need to understand what subtypes are actually benefiting. I don't think you can in an expeditious manner be exploring dose effects and subtype effects, so picking whichever agent. I

would say the benefit is because this is one sponsor, they can pick, but you could have a rational decision to which one it is and try to enrich, and then pick.

As I've said before, I do think you can establish a bar, a benchmark, in a futility analysis with an objective response rate that needs to be high, looking at what's ultimately led to survival benefits and whether that's 50 percent, 60 percent, 80 percent, but clearly it's not 20 or 30 percent. So I think if it can't meet a high bar, it's futile, so we get this answer pretty soon.

DR. CHEN: Thank you for your comments.

Dr. Vinks, you haven't been able to ask a question for a while. Do you have some comments?

DR. VINKS: Yes. Alexander Vinks, NDA Partners. As a clinical pharmacologist on this committee and temporary member, I just want to reiterate that there are some opportunities to maybe improve on a drug that, as was said, was developed quite suboptimally. I think, as

Dr. Spratt said, it's not only about dose, but also, given the large heterogeneity, I think there can be a lot learned from what has been seen in patients before, with presentations on registries where there are data.

I think going back to the data and using -- I work in the space of modeling forum drug development, and I've seen tremendous results of applying modeling and simulation and more qualitative approaches using all the available data to come up with more insight that would inform them; for instance, a smaller study that would give us, in a subset of patients, confirmatory data, as opposed to this, what I see as a very large, traditionally organized, long clinical trial with a control group, where I hear clinicians say, "I'm not very excited if I see that." So that definitely will not encourage enrollment in a study that is projected to take at least 7 years.

So I would encourage the sponsor to think about this, and go back to all the data that are available, and come up with better insight in both

the pharmacology/biology, combine that, and also look at exposure response to pin down what is a most likely, say, smaller study that could be simpler but still get robust informative data. Thank you.

DR. CHEN: Thank you.

Dr. Rosko?

DR. ROSKO: Ashley Rosko, Ohio State. It is clear from our panel discussion here that there are many more questions than there are answers. I think when I'm looking at both of these questions -- and these are my comments about this -- I'm a hematologist, and working in T-cell lymphoma, it's a very rare disease, and high acuity as well, so enrolling patients into clinical trials is very difficult. At the same time, when it comes to having very little treatment options for this patient population, taking away those drug options for patients I think is uncertain.

But I also think that part of this discussion is the fact that, according to the slides, this very long length of time, the FDA is

being transparent as well, saying this was something that should never happen again. As such, this FDORA legislation has been put in place to allow us the authority to not have these prolonged delays when it comes to allowing trials to come to the postmarketing phase. I think that's very transparent on the FDA's part to say, here's what we've done to be able to make sure this doesn't happen again.

Then moving forward, I just think it's a great opportunity to allow the FDA and industry to partner to say, here's what you've done so far since 2019, since you've acquired this drug. We want to allow industry to work in rare diseases because we need that, and here are ways for us to be able to work together to allow -- whether it's a second trial in a relapsed setting that's happening concurrently with the active trial -- these drugs, and for patients to have access to them moving forward.

So when I think about these strategies to promote timely completion of the trial, I think

this is the discussion, if the FDA and the sponsor are in a place, to say are we doing everything that's possible to allow these studies to move forward and to allow patients to have access to these drugs? I think those open discussions should be ongoing to make sure that they are working with their CROs and they are creating access to patients; that is very tough to be able to reach such an uncommon patient population and that they're doing more in order to allow for patients to have access to the therapies.

So that's my opinion when it comes to the discussion that's happened here today.

DR. CHEN: Thank you.

Dr. Thanarajasingam?

DR. THANARAJASINGAM: Yes. Thank you. I just as a clinician want to emphasize, and somebody who's a lymphoma-specific hematologist, there was some discussion about withdrawal of these agents now. We have so little right now in this space that I would not recommend withdrawal of these agents right now. We do use them both. We use

whatever we have at our hands in a sequential manner, and we're capable of addressing risks and uncertainties with our patients while we're in this prolonged vulnerability period while we get some confirmatory data on a reasonable time frame going forth.

Ninety-five percent of patients in our country are not treated on clinical trials, an issue that the FDA, and NCI, and us in academia and industry are hard at work on, but I don't think it's fair to patients who are not able to access trials to have withdrawal of potentially active agents that were on the market because of a lack of due diligence from the sponsor, without some form of confirmatory trial.

I appreciate that there's going to be muddling of survival endpoints when people can get these things in the second line, and I have expressed concerns about the feasibility of accrual in the front-line trial, even with the long time frame that's been proposed. So I want to affirm the earlier discussion about trying to do

this additionally in a smaller study in the relapsed/refractory setting to get an earlier readout in the population where we need this, ideally in some of the suggestive histologies; and I think that this suggestion of trying to problem solve confirmatory trials in the original population is appropriate for future accelerated approvals, and we'll also get dose optimization, as well, which I think is very important, as emphasized by Project Optimus.

But I do acknowledge it's not easy. My patient from South Dakota, who lives 9 hours away driving to see me, is not going to want to be here on a weekly basis for a clinical trial therapy if they can get the same thing from their local oncologist, so that underscores the challenge of doing trials when the agent's already been approved. But how can we incentivize patients and clinicians to participate? There have got to be ways, and I think we need to innovate, and problem solve, and we have an obligation on behalf of the patient struggling with these diseases to do that.

I appreciate the discussion today, and thank you for letting me be part of it.

DR. CHEN: Thank you.

Dr. Spratt?

DR. SPRATT: Because this is a committee discussion, I figured I would converse with the committee. While I very, very much respect the prior speaker's insights and obviously personal experience, I guess my challenge also as a clinician is, with romidepsin, clinicians had the option to say that they are experts to be able to give these recommendations to patients, but without the confirmatory data, you're left with beliefs and the half truth. So I'm sure in these clinics, people were prescribing this agent, to then realize a near doubling of grade 4 toxicity without improvements in PFS or overall survival. So I don't think it's as simple as clinicians, even expert clinicians. We wouldn't run trials if we weren't able to know what benefit them or not.

DR. THANARAJASINGAM: Can I just respond briefly to that?

DR. CHEN: Please go ahead.

DR. THANARAJASINGAM: I'm affirming my agreement with you 100 percent. I'm not saying that this substitutes the need for a confirmatory trial. A confirmatory trial must be done. I think we're all looking for ways that that could be done to get a faster readout and more accountability, and giving the FDA more authority to check in on is this actually happening, this accrual to the currently proposed trial. If it's not, are you trying to do this in the relapsed/refractory setting, and what is the time frame of that?

So I absolutely did not mean to imply that there should not be a confirmatory trial. I 100 percent agree with you that there should.

DR. CHEN: Thank you.

Dr. Choueiri?

DR. CHOUEIRI: Yes. Toni Choueiri, Dana-Farber. I think a lot of folks have suggested getting some sort of a randomized trial back fast. Since the drug we know has a response-rate benefit at least, is there a way to have an interim

analysis based on response and target the response difference; and if this is not met, the study stops? I think, based on responses and the need to confirm responses, this will buy us time, and it will be achieved faster, but obviously it's a higher risk. Thank you.

DR. CHEN: Thank you. Yes. We're not having the sponsor respond in this portion, but my understanding is they are planning interim analyses. I don't remember the exact number of events they are waiting for the interim analysis, but that was under their consideration.

Would any other panel members have other comments or questions before we start wrapping up?

(No response.)

DR. CHEN: Okay.

We will go back. Can you scroll back to question 1, please?

In terms of the delays in the post-approval confirmatory trials and whether the current plan to verify the clinical benefit is reasonable, considering the sponsor's proposed timelines, I

think the consensus of the advisory committee is that we have significant concerns about the very prolonged delay in getting these confirmatory studies underway. We also have concerns about the dosing and whether or not these are the appropriate studies to be doing; or that there should be an additional study in a subset of T-cell lymphoma or in the relapsed/refractory setting has been brought up as well. We would like the FDA and sponsor to strategize about other possible ways to have a shorter study readout than waiting another 7 years from now, which would be essentially 20 years from the initial approval of pralatrexate.

Can we go on to question 2?

In terms of strategies to promote timely completion of the confirmatory trials and insights from this experience that may facilitate completion of future accelerated approvals, we note that there has been a major change in the regulatory and legal landscape for accelerated approvals, and the committee fully supports the changes that have been made for confirmatory studies to be underway at the

time of accelerated approval. So we note that there is a marked difference in the timeline in those studies when the confirmatory studies were already underway at the time of accelerated approval, and that is something that will be certainly helpful for the future and the regulations that have been promulgated from that.

Going back in terms of the timely completion of this particular study for pralatrexate and belinostat, this goes back, in part, to question 1, and again, the committee does have significant concerns about the long timeline to the approval of these -- to expect the completion of these studies, should I say -- and that it may be better served to do a study in a smaller population where there might be a greater chance of benefit, and also to think about doing a study in the relapsed/refractory population, whether it's versus dealer's choice or something else along those lines, to try to see if we can get a faster readout. But we do have concerns about the dosing and with the toxicities that have been seen with

these agents, so it is a bit of a mixed bag that we do not have a direct answer for this.

I would also like to note that the question for this committee from the FDA is different from the typical ODAC. We are not being asked to approve or revoke approval for this drug. There is not on the agenda that we are talking about removing the drugs from the market at this time.

Does the FDA have any other questions or concerns?

DR. RICHARDSON: Hi. This is Nicholas Richardson from FDA. No further questions or concerns. Just in closing, we'd really like to thank the committee for their thoughtful discussion today on this important topic for patients. We truly appreciate it.

Adjournment

DR. CHEN: I would like to thank all the participants and thank you for your participation. We will now adjourn the meeting. Thank you.

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