FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC)

Wednesday, December 18, 2019

8:00 a.m. to 11:56 a.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. HOFFMAN: Good morning. I'd first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Brittney Manchester. If you're present -- yes, you are -- please stand. Thank you.

My name is Phillip Hoffman. I'm the chairperson for this meeting. I'll now call the morning session of today's meeting of the Oncologic Drugs Advisory Committee to order. We'll start by going around the table and introduce ourselves. We'll start with the FDA to my left and go around the table.

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

DR. THEORET: Good morning. Mark Theoret, deputy office director, Office of Oncologic

Diseases and associate director of immunotherapeutics in the Oncology Center of Excellence, acting.

DR. LEMERY: Steven Lemery, acting director, Division of Oncology III.

DR. WARD: Ashley Ward, clinical team leader.

DR. DOROS: Leslie Doros, clinical reviewer.

DR. KLEPIN: Heidi Klepin, geriatric oncologist, Wake Forest School of Medicine.

DR. HINRICHS: Christian Hinrichs, principal investigator, NCI.

DR. HALABI: Susan Halabi, biostatistician, Duke University.

DR. HOTAKI: Lauren Hotaki, designated federal officer.

DR. HOFFMAN: Philip Hoffman, medical oncologist, University of Chicago.

DR. CRISTOFANILLI: Massimo Cristofanilli, breast medical oncology, Northwestern University, Chicago.

DR. ULDRICK: Thomas Uldrick, medical

oncology, Fred Hutchinson Cancer Research Center.

DR. SUNG: Anthony Sung, Duke University, hematology-oncology.

MS. WEBB: Kimberly Webb. I'm the patient caregiver, a representative. My son was diagnosed with epithelial sarcoma. I'm also the admin for our epithelioid sarcoma Facebook pages. We have three of them, and we represent -- there's over a thousand members, so I'm trying to represent them as well.

DR. MEYER: Christian Meyer, medical oncologist, adult sarcomas, Johns Hopkins.

DR. RIEDEL: Richard Riedel, sarcoma medical oncologist from Duke University Medical Center.

DR. CHENG: Good morning. Jonathan Cheng, medical oncologist, industry rep. I'm with Merck.

DR. HOFFMAN: Dr. Tap from Cornell is going to be joining by phone, but we'll mention when he joins.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held.

Our goal is that today's 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 when recognized by the chairperson. We look forward to a productive meeting.

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

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

Now, I'll pass the microphone to Dr. Lauren Hotaki, who will read the Conflict of Interest

Statement.

Conflict of Interest Statement

DR. HOTAKI: The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee under 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 his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest 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.

The committee will discuss new drug

application 211723 for tazemetostat tablets submitted by Epizyme, Inc. The proposed indication used for this product is for the treatment of patients with metastatic or locally advanced epithelioid sarcoma not eligible for curative surgery.

This is a particular matters meeting during which specific matters related to Epizyme's NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that the 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 Merck and Company.

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

DR. HOFFMAN: We will now proceed with the FDA's introductory comments from Dr. Ashley Ward.

FDA Opening Remarks - Ashley Ward

DR. WARD: Members of the advisory committee, of the Epizyme team, invited guests, visitors, and FDA colleagues, good morning. My name is Ashley Ward. I'm a pediatric oncologist in the Office of Oncologic Diseases, and I'm the cross-disciplinary team leader for the tazemetostat

new drug application. Epizyme is seeking accelerated approval of tazemetostat for the treatment of patients with metastatic or locally advanced epithelioid sarcoma who are not eligible for curative surgery.

As you will hear today, epithelioid sarcoma is a rare malignant soft tissue sarcoma that accounts for less than 1 percent of all soft tissue sarcomas. The NCI estimates that there are approximately 125 new cases of epithelioid sarcoma diagnosed in the United States every year. Patients are typically diagnosed between 20 and 40 years of age, and there's a 2 to 1 male preponderance. There is a high propensity for local and regional spread of the disease, and approximately 50 percent of patients have metastatic disease at the time of diagnosis.

Patients with metastatic disease have a reported 5-year survival of 0 percent. Epithelioid sarcoma is distinguished from other soft tissue sarcomas by characteristic pathology findings and distinct immunohistochemical or IHC staining.

Approximately 90 percent of cases of epithelioid sarcoma show nuclear loss of INI-1 by IHC.

Wide surgical excision is the mainstay of treatment for localized disease. Neoadjuvant or adjuvant radiation therapy is often administered to reduce local relapse, but systemic chemotherapy is typically reserved for advanced stage disease. Although there are no therapies approved specifically for patients with epithelioid sarcoma, doxorubicin and pazopanib are both approved for the broader population of patients with soft tissue sarcoma and are administered to patients with epithelioid sarcoma.

The FDA clinical reviewer, Dr. Doros, will describe the approvals of doxorubicin and pazopanib and their use in patients with epithelioid sarcoma in greater detail. Both Epizyme and the FDA will highlight the inadequacy of available therapies for patients with most forms of soft tissue sarcoma, including epithelioid sarcoma.

Tazemetostat is a first-in-class orally administered small molecule inhibitor of the

methyltransferase enhancer of zeste homolog 2, otherwise known as EZH2. Epizyme postulates that tazemetostat acts by restoring balance to a set of proteins involved in chromatin remodeling and gene expression in tumors that have lost the tumor suppressor gene INI-1. However, the result and impact on the biology of epithelioid sarcoma is not well understood.

As Dr. Doros will explain in more detail, the observation that tazemetostat appears to have more robust activity in tumors with gain of function EZH2 mutations than it does in tumors with loss of INI-1 may indicate that INI-1 loss is not a reliable predictor of a response to tazemetostat and that the target of tazemetostat may be less relevant for cancer cell survival in epithelioid sarcoma.

The data submitted by Epizyme to support the safety and efficacy of tazemetostat in patients with epithelioid sarcoma come from Study EZH2, an ongoing non-randomized trial of tazemetostat in patients with various tumor types. You will hear

more detail about the design of this trial shortly.

Epizyme submitted the efficacy and safety results of Cohort 5, which enrolled 62 patients with epithelioid sarcoma as the primary basis on which they're seeking approval of tazemetostat in this indication. The FDA clinical reviewer, Dr. Doros, will also describe Cohort 6 in some detail. This cohort had very similar eligibility criteria and enrolled an additional 44 patients with epithelioid sarcoma. FDA considers that Cohort 6 is in some sense a repeat experiment that adds relevant information to the assessment of the efficacy of tazemetostat.

In Cohorts 5 and 6, the overall response rate, according to independent review using RECIST version 1.1 criteria, was similar at 15 percent and 11 percent, respectively. Pooled analysis demonstrated an overall response rate of 13 percent. The pooled duration of response ranged from 3.5 months to more than 24 months, also similar across cohorts. You will hear in detail how these results compare to those of therapies

currently used to treat patients with epithelioid sarcoma, as well as the limitations of these comparisons later from Dr. Doros.

The most common adverse events experienced by patients enrolled in Cohort 5 were pain, fatigue, and GI symptoms. Forty-eight percent of patients experienced a grade 3 or 4 adverse event and 37 percent of patients had a serious adverse event. It is important to note that these adverse events are not necessarily all attributed to tazemetostat. One of the limitations of a single-arm trial is that it is not possible to determine whether individual adverse events are present at a higher frequency in patients who receive tazemetostat than those who do not, and thus establish a causal relationship.

Although 34 percent of patients required a dose interruption for toxicity, dose reductions and discontinuations of tazemetostat for toxicity were uncommon. The adverse event profile associated with tazemetostat will be discussed in more detail by both Epizyme and the FDA.

As you will hear, an important risk of tazemetostat is the risk of secondary malignancies associated with its use. In the pooled safety population of 822 adult and pediatric patients with solid tumor or hematologic malignancies, 6, or 0.7 percent, developed secondary myelodysplastic syndrome, acute myeloid leukemia, or T-cell lymphoblastic lymphoma.

As T-cell lymphoblastic lymphoma occurred in juvenile and adult rats during 13-week toxicology studies and EZH2 loss-of-function mutations have been identified in patients with spontaneous hematologic malignancies, the development of secondary malignancies may be an on-target effect of tazemetostat.

Epithelioid sarcoma is a very rare cancer. Most of the agents used to treat epithelioid sarcoma are chemotherapeutic agents associated with low response rates and substantial toxicities, and there is a need for new therapies with a favorable risk-benefit profile.

The FDA commends Epizyme for exploring

tazemetostat as a potential therapy for epithelioid sarcoma, however, Study EZH-202 yielded an overall response rate of just 11 to 15 percent, with a 95 percent confidence interval showing that the true response rate may be as low as 4 to 7 percent.

While the applicant will argue that a large fraction of patients had durable, stable disease, the FDA does not consider stable disease to be a reliable endpoint in a single-arm trial, as it is not possible to assess whether any observed period of stable disease is due to drug effect or represents the natural history of the patient's tumor.

Given the limited clinical experience with tazemetostat and lack of comparative data, FDA brought this application to the Oncology Drugs Advisory Committee to enable public discussion of the results of EZH2 and whether the evidence is sufficient to demonstrate the benefit of tazemetostat in patients with epithelioid sarcoma.

A key uncertainty regarding the application is whether the low response rate observed on EZH-

202 will translate into a positive impact on survival or other clinical benefit. Epizyme is planning a randomized confirmatory trial of tazemetostat with doxorubicin compared to doxorubicin alone in patients with epithelioid sarcoma. This may address this uncertainty, however, enrollment to this trial has not yet begun.

At the end of the discussion period, the ODAC will be asked to vote on whether the demonstrated benefit of tazemetostat outweighs the risks of the drug in the proposed indication. This concludes my remarks, and I thank you for your attention.

DR. HOFFMAN: Thank you.

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 sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interest and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking. We will now proceed with the applicant's presentations.

Applicant Presentation - Shefali Agarwal

DR. AGARWAL: Good morning. Mr. Chair, members of the ODAC, and the FDA, thank you for the opportunity to present the data supporting the accelerated approval application for tazemetostat for the treatment of patients with metastatic or locally advanced epithelioid sarcoma. I am

Dr. Shefali Agarwal, the chief medical officer at Epizyme.

Epithelioid sarcoma is a rare and aggressive soft tissue sarcoma with about 120 new cases per year. Epithelioid sarcoma is very difficult to treat and demonstrate lower objective response rate than attainable in other soft tissue sarcomas. Our application suggests that patients with locally advanced or metastatic epithelioid sarcoma have a median overall survival between 10 and 16 months. All will eventually die from this serious cancer in 5 years or less.

Tazemetostat is a promising novel oral therapy with both efficacy and safety advantages for patients with metastatic or locally advanced epithelioid sarcoma. While tazemetostat demonstrates a similar or better overall response rate to standard of care therapies, both the median duration of response and the median overall survival are longer.

For tazemetostat, the median DOR was 16.4 months and some patients achieved durable stable

disease. The median overall survival was 19 months, and some patients achieved a clinical benefit after the disease progression, which may be linked to the time it takes for an epigenetic therapy like tazemetostat to stabilize and shrink tumors. This unique benefit shows that overall response rate alone is insufficient to fully define clinical benefit.

Additionally, tazemetostat is well tolerated with advantages over standard of care. Unlike those options, the tolerability allows patients to remain on therapy. Adverse events led to very few discontinuations and dose reductions. Given that Epizyme's tazemetostat study is the fourth prospective epithelioid sarcoma study, it's important to compare it with the published retrospective cases of patients with epithelioid sarcoma.

The overall response rate ranged from 0 to 27 percent. We agree with the FDA regarding the limited nature of the existing literature and that these rates are likely inflated. The true response

may be less than reported because these small studies may not have used RECIST criteria, and they largely include patients with locally advanced disease. In contrast, the tazemetostat study had a majority of patients with metastatic disease and used RECIST criteria.

Regardless of an ORR of zero, or 27 percent, those responses are typically of short duration with a median DOR of less than 2 months and resulted in a median overall survival of between 10 and 16 months. These results highlight the value of a new therapy like tazemetostat that can provide a similar or better objective response, the opportunity for disease stabilization, significantly longer DOR, and longer overall survival.

As seen with other epigenetic therapies, tazemetostat needs time to achieve the maximum effect. As a selective, potent first-in-class inhibitor of histone methyltransferase EZH2, it targets a known oncogenic driver. In an epithelial sarcoma cell line, it took about 7 days for

tazemetostat to show cell growth inhibition, which was further enhanced over the next 7 days. This is unlike chemotherapy that works within a day.

There are many steps within EZH2 inhibition and an antiproliferative effect, including effects on DNA replication, NmRNA, and protein production before ultimately resulting in a delayed response. In summary, tazemetostat needs time to elicit benefit, which is supported by this preclinical data.

Looking more closely at tazemetostat's normal mechanism of action, in normal cells, the SWI/SNF complex restricts PRC2 function, to coordinating expression, and to regular normal cell growth. This is important for keeping EZH2 activity in check to prevent uncontrolled cell growth, however, SWI/SNF can be rendered dysfunctional if one of its key proteins is lost. One such key protein is INI-1.

When INI-1 is lost, there is aberrant EZH2 activity. This can lead to uncontrolled cell proliferation and ultimately an oncogenic

dependency on EZH2. This is one of the mechanisms that is essential for tumor growth in epithelioid sarcoma. Tazemetostat works through a potent and selective inhibition of EZH2. Thus, with tazemetostat, we have a strategy for killing tumor cells that are dependent on EZH2.

The proposed indication for tazemetostat is for the treatment of patients with metastatic or locally advanced epithelioid sarcoma who are not eligible for curative surgery. Let me summarize how the data we will present today fulfill the three criteria for accelerated approval.

First, epithelioid sarcoma is a serious, life-threatening and rare malignancy with few effective treatment options. Second, tazemetostat does provide a meaningful advantage over existing therapies that extend just beyond ORR. The median duration of response is about twice as long and mean overall survival was 3 months longer than previously reported.

As you will see, patients can achieve and maintain clinical benefit even after radiological

progression, contributing to improvements in tumor burden, and unlike available therapies, tazemetostat is well tolerated with a favorable safety profile. This alone provides a meaningful advantage. We believe that tazemetostat's epigenetic effect on long-standing stabilization of disease is reasonably likely to predict for clinical benefits. In addition, we have collaborated with the FDA to design a randomized placebo-controlled confirmatory study.

Here is the agenda for the presentation today. We also have additional external experts. All have been compensated for their time and travel. Thank you. I'll now turn the lectern over to Dr. Patel to discuss the unmet need.

Applicant Presentation - Shreyaskumar Patel

DR. PATEL: Thank you, Dr. Agarwal, good morning. I'm Shreyas Patel, medical director of the Sarcoma Center at the University of Texas MD Anderson Cancer Center. I've been treating sarcomas for the last 30 years. I've seen firsthand the serious and urgent need for new

therapies for patients diagnosed with metastatic epithelioid sarcoma.

Let me begin by emphasizing just how high the unmet need is for patients with metastatic disease. Today, there are limited tolerable treatment options that provide prolonged tumor regressions and control tumor growth. Epithelioid sarcoma is mostly unresponsive to available chemotherapy and other agents that can be used fairly effectively to treat other solid tumors, including other soft tissue sarcomas.

This suboptimal state of science is compounded by the fact that this rare and incurable cancer mostly strikes young active people in the prime of their lives; and typically, like other rare diseases, the journey to a proper diagnosis can be long, which can allow the tumor to progress and metastasize.

Epithelioid sarcoma is a rare soft tissue sarcoma representing only 1 percent of all cancer diagnoses in adults of which epithelioid sarcoma comprises less than 1 percent, and the disease

typically affects patients between 20 and 40 years of age. Epithelioid sarcoma can present in a number of challenging ways. They can be bulky. They can appear in challenging locations such as in major organs and serosal membranes, and there also may be numerous small metastatic lesions.

By the time most patients receive a definitive epithelial sarcoma diagnosis, their disease is late stage, patients have a very poor prognosis, and ultimately die from this fatal disease. In fact, almost 50 percent of patients will be diagnosed with metastatic disease and surgery is no longer an option.

It is important to distinguish early-stage epithelioid sarcoma from metastatic epithelioid sarcoma. While the FDA briefing document characterizes epithelioid sarcoma as slow growing, the patients being discussed today have metastatic disease, and this late-stage disease does show rapid growth. The reported 5-year survival rate in patients with metastatic or locally advanced disease is approaching zero percent with median

overall survival of 10 to 16 months.

Here is an example of a patient with metastatic epithelioid sarcoma with tumor in the chest that demonstrates rapid disease progression despite currently available treatments. We can also see how tumor location can present some unique challenges.

This is a baseline CT scan of the chest of a patient with bulky bilateral hilar metastasis. Six weeks later on standard chemotherapy, the disease progressed at a relatively rapid pace. We also know that progressive metastatic disease can be associated with worsening of symptoms, in this case progressive shortness of breath and gradual clinical decline.

A treatment that could induce durable stabilization of disease would benefit this patient, but unfortunately we only have a few options to offer patients with locally advanced or metastatic disease. None have been approved specifically for epithelioid sarcoma, and all have limited efficacy and serious safety risks.

There are two FDA-approved therapies for the broader category of soft tissue sarcomas and used in patients with advanced epithelioid sarcoma, doxorubicin and pazopanib. Neither have demonstrated impressive efficacy in epithelioid sarcoma. Gemcitabine and docetaxel are also used off label for soft tissue sarcomas.

Epithelioid sarcoma is more treatment resistant than most other variants of soft tissue sarcomas. This makes comparing response rates between epithelioid sarcoma and the broader category of soft tissue sarcomas unreliable, and serious safety risks, including cardiotoxicity, severe myelosuppression, and hepatotoxicity force many patients to discontinue these therapies.

In summary, patients with metastatic or locally advanced epithelioid sarcoma have an immediate need for a novel therapy that offers efficacy, safety, and tolerability, allowing them to stay on therapy for an extended period of time. This rare disease is frequently diagnosed late when the tumors are unresectable. These patients are

generally young and often otherwise healthy. Durable treatment options that would stabilize disease for these patients would be a meaningful clinical benefit. Unfortunately, with such a small patient population and little innovation, no available therapies address these needs.

Thank you, and Dr. Agarwal will now present the efficacy results for tazemetostat, which responds to this urgent need for these patients.

Applicant Presentation - Shefali Agarwal

DR. AGARWAL: Thank you, Dr. Patel.

I will review the efficacy results for tazemetostat that demonstrate clinically meaningful and durable responses for patients with metastatic or locally advanced epithelioid sarcoma. The primary evidence of efficacy supporting our application comes from Study 202. This is an ongoing phase 2, open-label, single-arm study of tazemetostat in patients who have been placed into 1 of 7 cohorts, based on their specific type of cancer.

As discussed with the FDA, our focus today

is on Study 202, Cohort 5, which we will refer to as the primary epithelioid sarcoma population since it's the primary cohort for evaluating efficacy in the NDA. Of note, Cohort 6 in patients with epithelioid sarcoma was added after initiation of Cohort 5. The data were only recently shared with FDA, and the cohort is not yet mature.

Study 202, Cohort 5 is the first prospective study to evaluate patients with locally advanced metastatic epithelioid sarcoma. These patients were treated with 800 milligrams of tazemetostat twice daily. A total of 62 patients were enrolled, 59 adult and 3 pediatric. Investigators evaluated objective response every 8 weeks using RECIST 1.1 criteria. A blinded central independent review committee, or IRC, also reviewed all radiology scans in chronological order. The IRC assessments were used to determine clinical response.

The protocol explicitly allowed patients assessed as having progressive disease, based on RECIST criteria, to continue tazemetostat. This decision was made at the discretion of the

investigator in consultation with the patient if they perceived an ongoing benefit from therapy. For example, a new lesion would signify disease progression even when the tumor burden had stabilized or reduced.

These patients continue to be evaluated every 8 weeks for as long as they remain on therapy, but they were not included in the efficacy analysis after first progression. Patients remaining on tazemetostat did not receive concomitant antineoplastic therapy. The primary endpoint was objective response rate, including complete and partial responses. Secondary endpoints included duration of response, disease control rate, progression-free survival, and overall survival.

Moving to demographics, Cohort 5 included a mostly male young adult population that is representative of a real-world patient with epithelioid sarcoma. Median age was 34 years and most patients were white. Seventy-one percent had advanced disease at the time of their diagnosis and

94 percent had metastatic disease at study entry. Ninety-five percent of patients had progressive disease prior to study entry with a median time from last progression of 1.4 months. Median diameter was 58 millimeters and tumor ranged from 11 to 218 millimeters.

The type of prior cancer-related therapies were consistent with standard of care for epithelioid sarcoma. Most patients had undergone cancer-related surgical procedures. Forty-two percent had undergone prior amputation or major resection and most received prior radiotherapy. Sixty-one percent had received at least one prior systemic therapy such as doxorubicin, but time on prior systemic therapy was short with a median duration of 2.4 months.

As of the data cutoff, 13 percent of patients remained on tazemetostat. The primary reason for discontinuation was disease progression, either radiological or clinical. Importantly, only 2 percent of patients discontinued due to an adverse event.

Looking next at the primary endpoint results, 15 percent of patients achieved a primary endpoint of a complete or partial response, demonstrating meaningful activity of tazemetostat in patients with epithelioid sarcoma. Since 95 percent of these patients had progressive disease at study entry, this represents a meaningful reduction in tumor burden.

Importantly, 21 percent of patients achieved disease control beyond 32 weeks. Let's more closely look at these results. A total of 63 percent of patients achieved a complete response, partial response, or stable disease as their best response during the study. This included 1 patient with a complete response and 8 patients with partial responses.

When looking at the percent change in target lesion diameter in this waterfall plot, 68 percent of patients had a reduction in tumor burden. Remember that the majority of patients entered the study with advanced stage progressive disease, so this plot provides strong evidence of the direct

effect of tazemetostat on this serious disease.

In the 9 patients achieving a complete or partial response, responses were durable. The median duration of response was 16.4 months or 69.7 weeks with approximately 60 weeks of follow-up. Keep in mind that the median survival is usually less than one year. This duration of response is important, but only tells part of the story for an epigenetic therapy that takes time to demonstrate an effect; so we will examine individual responses by looking at percent change in each patient's target lesion diameter on the Y axis for time in the next series of slides.

Here is the starting spaghetti plot of the full Cohort 5 ITT population segmented by best overall response. As you can see, the majority of these patients saw stabilization or reduction in tumor burden. Let's review the tumor burden based upon the response.

Here are the 9 patients with an objective response, showing sustained benefit in tumor burden with a median DOR longer than previously reported.

The median time to response was 17.1 weeks. This highlights the importance of a well-tolerated treatment option that allows patients to remain on therapy long enough to achieve a response, but let's look at those patients without an objective response.

Beginning with the 30 patients with stable disease, 10 of the 30 stable disease patients chose to continue therapy post-radiological progression, shown by the red diamonds. On each of these patients, the investigator stated that they perceived a continued clinic benefit, as can be seen by the stabilization in tumor burden. Two of these patients remained on therapy for over 18 months. There were another 2 stable disease patients that remained on therapy for well over a year. Although neither achieved a clinical response, they also did not experience disease progression and would remain on therapy at data cutoff.

We also saw indicators of clinical benefit in another 3 patients who discontinued tazemetostat

and appeared to have reduced tumor burden. Two patients showed a reduction in the target lesion size but discontinued therapy at disease progression. The third was censored as a patient due to pursue surgery.

If we combine these patients, 15 of the 30 patients, or half, with stable disease appear to be gaining a benefit. These results align with expectations for an epigenetic therapy that takes time to affect the tumor burden. In some cases, patients regained a clinical benefit following progression.

Let's finally look at the 19 patients with progressive disease. In 5 of these 19 patients, the investigator and patient chose to continue tazemetostat because they perceived a clinical benefit. As you can see, 2 of the 5 remained on therapy for over one year, and one of those was continued on therapy at the time of data cutoff. We also saw indicators of potential benefit in other patients with progressive disease. In fact, another 3 patients appeared to have reduction in

their target lesions below the third threshold for a partial response or discontinued therapy due to progression.

Thus, we see 8 of 19 patients with progressive disease with indication of benefit. These data also suggest the potential epigenetic benefit after radiological progression. In fact, some patients who continued with tazemetostat post-RECIST progression actually achieved a partial response. In Cohort 5, 2 patients achieved a partial response in the original target lesions post-disease progression. While not included in the overall response rate, these results are clinically meaningful.

We also observed the same situation in Cohort 6. Two patients achieved a PR in their original target lesions post-RECIST progression. These observations reinforce that epigenetic therapies take time to achieve maximal benefit.

The prolonged benefit also appears to result in a median overall survival that is longer than previously published. Median overall survival was

at 19 months or 82.4 weeks. This exceeds the literature reported median overall survival of 10 to 16 months in patients with metastatic disease. Survival estimates at 32 and 56 weeks support the benefit of tazemetostat for the treatment of this rare and incurable cancer. At 56 weeks, the proportion of patients whom remained alive was 57 percent.

Next, we looked at the relation between overall survival and disease control rate. Study 202 showed alignment between disease control and survival, as shown. This analysis includes the 47 patients who are alive at week 32 and shows overall survival by week starting at 32 weeks. Patients are categorized into either disease control at 32 weeks, shown in blue, or no disease control at 32 weeks, shown in gold.

As you can see, there is clear separation between patients achieving disease control at 32 weeks and those who do not, with a p-value of 0.0236. This supports that disease control, including stable disease, at 32 weeks correlates

with overall survival. Let's now briefly review some results from Cohort 6 that were recently provided to FDA.

Overall, the data for Cohort 6 align with pivotal Cohort 5 results. Eleven percent of patients achieved an objective response with 14 percent attaining disease control to 32 weeks. Note these are interim analyses and 18 percent of patients remain on therapy. As of the data cutoff date, median duration response had not been reached. Median overall survival was 71.9 weeks, supporting the benefit of tazemetostat compared to chemotherapies.

Importantly, the spaghetti plot showing individual responses over time for Cohort 6 reveals the same delayed onset epigenetic benefit we just showed for Cohort 5 beyond just the ORR. Patients that continued tazemetostat appeared to gain a tumor burden benefit.

Based on the success of phase 2 study, Epizyme has initiated a large randomized, placebo-controlled confirmation study to data mine

tazemetostat's treatment effect on PFS. This study will provide the necessary evidence of clinical benefit for full approval.

Study 301 is a global, phase 3, multicentered, double-blind, placebo-controlled study in patients with locally advanced unresectable or metastatic epithelioid sarcoma. It will evaluate tazemetostat in combination with doxorubicin as frontline therapy. Patients will be randomized to receive tazemetostat metastatic plus doxorubicin or placebo plus doxorubicin for 6 cycles; then all patients will continue on monotherapy of maintenance of tazemetostat or placebo in a blinded fashion until disease progression, toxicity, or withdrawal.

In conclusion, tazemetostat's novel mechanism of action offers clinically meaningful benefit for these patients with this progressive, incurable disease. The primary epithelioid sarcoma population in Study 202 provides the first prospective data in patients with locally advanced and metastatic epithelioid sarcoma. The study was

able to demonstrate a 15 percent objective response rate supported by strong median duration of response of 16.4 months. This demonstrates the opportunity for prolonged benefit in patients at risk for rapid relapse, and importantly, 68 percent of patients had a reduction in tumor burden supporting tazemetostat's direct effect on this cancer.

Of patients who were progressing at the time of entry, 21 percent had disease control at 32 weeks, which we believe to be correlated with survival. Finally, tazemetostat continued to show benefit in patients even after RECIST progression. This highlights and important feature of the epigenetic mechanism of action. Thank you. Dr. Demetri will now present the safety results for tazemetostat.

Applicant Presentation - George Demetri

DR. DEMETRI: Thank you. I'm Dr. George Demetri, director of the Sarcoma Center at the Dana-Farber Cancer Institute in Boston, Massachusetts, and I'm an investigator on the

phase 2 tazemetostat study for epithelioid sarcomas. I'd like now to present the safety profile for tazemetostat.

Tazemetostat has a favorable safety and tolerability profile that differs from currently available sarcoma therapies. Adverse events are easily manageable with a low rate of discontinuations. Unlike what we see with current standards of care, tazemetostat enables patients to stay on therapy. We saw no clinically significant nor fatal cardiotoxicity, nor hepatotoxicity.

My presentation will focus on the primary epithelioid sarcoma population as they best represent the safety profile that can be expected in patients with epithelioid sarcomas. In addition, tazemetostat has been evaluated in 686 adult patients with advanced malignancies, who received the proposed dose of 800 milligrams twice daily.

In the primary epithelioid sarcoma population, the median duration of treatment was 5.5 months. This is twice the treatment duration

compared to what we'd expect and sought from prior systemic therapy in this patient population. Almost half of the patients remained on tazemetostat for more than 24 weeks, which is also an indirect indication of tolerability.

Treatment compliance in Study 202 was high. Most patients took an average of 786 milligrams of the 800-milligram recommended dose, and 95 percent of patients took at least 90 percent of the doses. This compliance rate aligns with the tolerability profile and the favorable ability to remain on tazemetostat.

The overall tazemetostat safety profile in patients with epithelioid sarcoma is similar to the experience of all patients treated with the target dose of 800 milligrams twice daily. This also indicates a stable, predictable, and consistent safety profile for tazemetostat.

While all patients experienced some adverse event, less than half were grade 3 or 4 in severity, and only a small percentage of those were deemed related to therapy. About one-third of

patients required dose interruptions that appear mostly related to lab abnormalities rather than symptomatic adverse events, and importantly, only one patient needed a dose reduction. This is very uncommon with current anticancer therapies supporting a good tolerability profile.

Additionally, adverse events leading to discontinuations were very low, highlighting the fact that while adverse events do occur, they are readily managed, allowing patients to remain on therapy.

Here are the adverse events reported in more than 15 percent of patients. As you see, fatigue, nausea, and cancer pain occurred most frequently in the primary epithelioid sarcoma population. The frequency and nature of these events observed were consistent with those commonly seen in the treatment of metastatic or locally advanced epithelioid sarcomas. The most common grade 3 or grade 4 adverse events were anemia and weight decrease. There were no cases of neutropenia nor thrombocytopenia. Again, the nature and severity

of these events are consistent with those commonly seen in patients with this advanced disease.

All but two serious adverse events were assessed as unrelated to tazemetostat and attributed to the underlying disease and/or comorbidity. As expected in patients with metastatic epithelioid sarcoma, which affects the lungs and the pleura, the most common events where hemoptysis and pleural effusion. There were no deaths due to any adverse event in the primary epithelioid sarcoma population.

Let's move now to review of the identified potential risk of secondary malignancies. Secondary malignancies were infrequent across the entire development program of this agent, and there were no reports in the primary epithelioid sarcoma population.

Across the program, through the most recent data cutoff, there have been 6 cases of secondary malignancies reported in 849 patients exposed or less than 1 percent. There was one pediatric patient with T-cell lymphoblastic lymphoma and

5 patients with myeloid malignancies. Let me review each of these cases in more detail.

Epizyme considers the risk for T-cell lymphoblastic lymphoma to be largely concentrated in pediatric patients based upon the higher drug exposure in these patients and the intact T-cell precursor compartment in pediatric patients from which T-LBL is derived.

This patient was a 9-year-old female who had a diagnosis of chordoma and developed this secondary malignancy on study day 432 after achieving a complete response, and the T-LBL subsequently resolved. She remains alive today. This case of T-LBL may be related to tazemetostat, though, based on EZH2 literature and nonclinical safety data. Based on this finding, the tazemetostat dose used in the Epizyme pediatric studies has subsequently been reduced to 520 milligrams per meter squared twice daily.

All of the patients with myeloid malignancies had other risk factors. One patient had MDS/MPN. One had lower risk MDS that

progressed to AML. One had a higher risk MDS and two developed AML. All five occurred after prolonged exposure between study days 441 and 842. All of these patients had factors in their medical history that predisposed them to these malignancies and confound interpretation. All patients had prior systemic and/or radiotherapy. At baseline, one patient had preexisting dysplastic changes in the bone marrow and two had hematologic abnormalities.

In carefully analyzing each of these cases, the risk for myeloid malignancies with tazemetostat treatment remains unclear. Furthermore, since 4 of the 5 events were in lymphoma, the risk observed is consistent with what has been seen in an overall lymphoma population. Nonetheless, with this uncertainty, it is prudent to include a warning in the label regarding increased risk for secondary malignancies. Epizyme is recommending that patients be monitored for the possible development of these secondary malignancies.

In conclusion, though tazemetostat offers a

very manageable safety profile to the generally young and active patients with epithelioid sarcoma that allows them to stay on therapy long term, the safety profile of the primary epithelioid sarcoma population, with regard to the nature, frequency, and severity of the adverse events, is consistent with that sadly observed in the target dose adult population.

The fact that few patients discontinued or had to decrease their dose demonstrate tazemetostat's favorable toxicity profile. This overcomes significant safety barriers with currently available therapies. Thank you, and now Dr. Schwartz will provide his clinical perspective

Applicant Presentation - Gary Schwartz

DR. SCHWARTZ: Thank you, Dr. Demetri.

I'm Gary Schwartz, chief of the Division of Hematology and Oncology at the Columbia University Medical Center and deputy director of the Herbert Irving Comprehensive Cancer Center in New York. I've had decades of experience caring for patients with rare sarcomas, with epithelioid sarcoma in

particular. Based on data presented, as well as my experience using tazemetostat in the clinical trial program, it's my conclusion that the benefits of tazemetostat clearly outweigh the risks.

In studies of monotherapy, there is clear evidence that tazemetostat is active against epithelioid sarcoma. Tazemetostat conferred an overall response rate of 15 percent and a disease control rate at 21 percent. In addition, we saw that nearly 70 percent of patients had a reduction in their tumor burden, many with prolonged stable disease over the course of the study. This result is particularly significant given the fact that almost all patients entered the study at an advanced stage and had progressive disease.

When considering tazemetostat, benefit over current therapy, we need to consider both the objective response and the duration response. Here are reported rates for tazemetostat alongside recently published registration level studies using doxorubicin and pazopanib as monotherapy for soft tissue sarcomas. These enrolled a population most

similar to tazemetostat and are aligned with what I've seen in my 30 years of experience. Even if we assume that the reported ORR in soft tissue sarcomas with doxorubicin is similar to tazemetostat, we know the duration of response for tazemetostat is longer, with median duration of over 16 months.

In epithelioid sarcoma, it's also important to recognize that some patients on tazemetostat treatment benefit from prolonged stabilization of their progressive disease. For these patients, stopping the increase in disease burden from the progressive disease is a clinical beneficial event. When counseling patients, I discuss that tazemetostat is an epigenetic therapy, and its tumor shrinking effect can and often does take time. Prolong treatment also gives the opportunity to convert stable disease to a partial response in the target lesions.

As a non-cytotoxic therapy, patients are not exposed to debilitating adverse events; therefore, prolong treatment with tazemetostat is possible

with good tolerability. It's this duration that is so intriguing about tazemetostat. For example, we look at this time plot showing treatment for the 62 patients in Cohort 5, and it clearly shows the prolong treatment durations.

The 13 patients who achieved disease control through 32 weeks represent most of those with the longest duration of treatments, as represented by the blue lines at the top, but it's very important to note that some patients continue on tazemetostat following RECIST progression due to an ongoing benefit of their target lesions. These are the patients who have a red diamond at the time of RECIST progression and they continue treatment with tazemetostat.

Let's look more closely at the 17 patients who continued on tazemetostat post-RECIST progression, indicating that the patient and investigator believed there is an ongoing benefit. This includes 4 patients who attained disease control, shown in blue, and 13 patients who did not, shown in gray. In fact, three of the patients

who never achieved a response have remained on therapy for a year post-radiological progression, shown by the top 3 gray bars. This prolonged duration of treatment not only speaks to efficacy but also to the advantageous safety profile, which allows patients to stay on therapy.

It is remarkable to see just how well patients tolerated tazemetostat. Discontinuation due to adverse events are rare, with only one patient discontinuing, and only one patient required a dose reduction, which is almost unheard of with oncology therapies. This differs significantly from current therapies for epithelioid sarcoma.

In addition, tazemetostat offers an improved safety profile compared to current therapies for epithelioid sarcoma, which is known to be with cardiotoxicity, myelosuppression, and hepatic toxicity. In fact, most of the grade 3 adverse events were easily treatable and have little clinical impact on the patient. The grade 4 SAEs are the real differentiator, showing an improved

safety profile with this drug over doxorubicin. In fact, only 2 patients reported an SAE deemed to be related to tazemetostat. In addition, we did not see cardiac dysfunction or neutropenia.

As we think again about these patients, keeping in mind just how young and active they tend to be, we know they could benefit from an easy to use convenient and tolerable therapy, and they often express great anxiety about having to endure chemotherapy. Not only the serious events with current therapies difficult to manage, they also can require clinic visits with dosing changes or IV administration, taking time from work or family. This is another benefit of tazemetostat, which is a convenient oral therapy that patients can take at home.

Before we conclude, I'd like to share the story of a patient who I think epitomizes how this new therapy could improve the care we can offer to patients with epithelioid sarcoma. Being diagnosed with a rare fatal tumor is a surprise for anyone, but doctors get cancers, and my patient was a

doctor. She had a lesion in the pelvis, and to resect it would have resulted in morbid surgery, so we elected to try to shrink the tumor first.

With the current options known to have limited efficacy and significant toxicities, she agreed to participate in a tazemetostat clinical trial. She achieved a near complete response, which allowed us to perform a resection of her residual disease with much less morbidity. In the absence of measurable disease, she actually went off therapy.

As often happens with this disease, it returned a year later, so we worked with the sponsor to allow her to take the drug again. With resumption of the therapy, she again attained a near complete response, remaining on therapy for over two years. During this time, she not only was able to function as a full-time physician and surgeon, she also gained a precious time that allowed her to have a surrogate baby.

I share this story not only because it was so meaningful to her, but also to me as her

treating physician. This demonstrates that tazemetostat, a drug with a new mechanism of action, benefits patients with limited options. There's an urgent need for patients with late-stage epithelioid sarcoma. We've been waiting for new and innovative therapies that offer both efficacy and safety, and that allow patients to tolerate and stay in therapy for an extended period of time.

Tazemetostat offers the opportunity for both responses and disease stabilization, and we should move to make it broadly available now under the accelerated approval pathway. Thank you.

Dr. Agarwal will now return to conclude.

Applicant Presentation - Shefali Agarwal

DR. AGARWAL: Thank you. My closing remarks summarize the benefits over existing therapy that support accelerated approval and a rationale for bringing a new option to this rare difficult to treat population. Tazemetostat is a promising novel oral therapy with both efficacy and safety advantages for patient with metastatic or locally advanced epithelioid sarcoma.

While the ORR is similar or better than what's been demonstrated with standard of care, the duration response and ability to achieve long-standing stable disease in these difficult to treat patients with progressive disease is clinically relevant, and we observed advantages in overall survival.

Furthermore, many patients continued to benefit from tazemetostat therapy even after radiographic progression. In fact, 4 patients in Cohort 5 and 6 achieved a threshold for partial response after RECIST progression. This is consistent with tazemetostat epigenetic mechanism of action.

Finally, the tazemetostat advantage that is most clear is safety. The tolerability profile allows patients to remain on therapy and benefit from the drug for an extended period of time without toxic or bothersome side effects seen with standard of care. Epizyme is confident that tazemetostat fulfills the threshold for accelerated approval in this rare patient population. Thank

you.

DR. HOFFMAN: Thank you very much.

Dr. Hawkins, would you just identify yourself for the record?

DR. HAWKINS: Dr. Randy Hawkins, Charles Drew University. And my apologies; the West Coast time got the best of me this morning.

DR. HOFFMAN: We'll now proceed with the presentation from the FDA, Dr. Doros.

FDA Presentation - Leslie Doros

DR. DOROS: Good morning. My name is Leslie Doros. I'm a pediatric oncologist, and I'm the clinical reviewer for the new drug application, 211723 for tazemetostat, submitted by Epizyme, who will be referred to as the applicant for the rest of the presentation.

The applicant has requested accelerated approval for tazemetostat for the treatment of patients with metastatic or locally advanced epithelioid sarcoma, who are not eligible for curative surgery. The proposed dosing regimen is 800 milligrams twice a day.

The key question the FDA has for the ODAC today is whether the data from Study EZH-202 provides sufficient evidence to establish the benefit of tazemetostat in patients with epithelioid sarcoma.

Study EZH-202 is an ongoing, multicenter, global, open-labeled, multi-cohort, non-randomized trial in patients with a variety of solid tumors. Cohorts 5 and 6 enrolled patients with epithelioid sarcoma. Cohort 5 originally had a two-stage design; where if at least one response was observed by week 24 in the first 15 patients, the study would enroll an additional 30 patients.

The study was amended to add an additional 30 patients to the original cohort if at least 5 responses were observed by week 24. The applicant submitted data from 62 patients who were ultimately treated on Cohort 5 as the basis for the new drug application. FDA also requested data from the 44 patients who were treated on Cohort 6 to aid in this review.

Efficacy and safety data from both cohorts

were submitted with the initial NDA using a data cutoff date of September 17, 2018. Upon receipt of this data, FDA noted that the ORR for Cohort 6 was just 5 percent. FDA acknowledged that the duration of follow-up for patients in Cohort 6 was shorter than that for Cohort 5. At FDA's request, the applicant provided an additional 10 months of follow-up data for this cohort during the review cycle. This updated data resulted in a similar time of follow-up for Cohort 5, based on the original submission, and Cohort 6, based on the updated submission.

Although Cohort 5 was intended to evaluate overall response rate and Cohort 6 was intended to assess the pharmacodynamic effects of tazemetostat on tumor immune priming, the eligibility criteria for both cohorts were very similar. The only differences were that demonstration of INI-1 loss was required for Cohort 5 but not Cohort 6. Consent for tumor biopsy was required for Cohort 6 but not for Cohort 5, and progression within 6 months of study entry was required for all

patients in Cohort 6 but only for some patients in Cohort 5.

The latter two differences are not expected to have notable impact on response rate, however, as the applicant postulates that the tazemetostat mechanism of action may be influenced by INI-1 loss, FDA acknowledges that this eligibility criteria could have an impact on response rate, which we will address shortly with a sensitivity analysis. Otherwise, as the baseline disease characteristics, patient demographics, median follow-up time, and efficacy results are similar between the two cohorts, FDA believes that Cohorts 5 and 6 represent sufficiently similar patient populations to allow pooled analysis of the data.

As previously mentioned, data from Cohort 5 was submitted by the applicant as the primary evidence of efficacy for this NDA. In this cohort, one patient experienced a complete response and eight experienced a partial response, leading to an overall response rate of 15 percent. In what was

essentially a repeat experiment in Cohort 6, one patient experienced a complete response and four experienced a partial response for an overall response rate of 11 percent. A pooled analysis of the two cohorts yields a response rate of 13 percent.

The applicant emphasized that many patients experience a best response of stable disease. As Dr. Ward stated earlier, a single-arm trial cannot be used to determine an effect on progression-free survival, as observed periods of stable disease may be due to the natural history of the tumor and not drug effect. The applicant also described a subset of patients who continued on therapy past progression. It is important to note that the fact that these patients stayed on tazemetostat so long highlights the lack of alternative available therapies rather than any benefit conferred by tazemetostat.

The pooled duration of response ranged from 3.5 months to more than 24 months and was similar across cohorts. A total of 7 patients had an

ongoing response at the time of the data cutoffs for Cohorts 5 and 6. Of the 14 patients that experienced a response, 9 had a response lasting 6 months or longer, and 4 had a response lasting 12 months or longer. Given the small number of responding patients, FDA does not consider median duration of response, as estimated by Kaplan-Meier methods, to be a useful summary measure.

FDA performed post hoc sensitivity analyses by subgroup to look for potential differential treatment effects, although the small sample sizes means that the results should be interpreted with caution. FDA notes that ORR appears to be similar across the original and expansion portions of Cohort 5 and regardless of number of lines in prior therapy. As FDA acknowledges that Cohort 6 allowed enrollment of patients with tumors that retained INI-1, FDA conducted a sensitivity analysis to determine whether this may have impacted response rate.

A total of 4 patients with retained INI-1 enrolled on Cohort 6. None of these patients had

an objective response. If these 4 patients are removed from the analysis, the ORR for Cohort 6 is 12.5 percent. Therefore, the inclusion of patients with retained INI-1 does not appear to have substantially affected the reported ORR in this cohort.

However, it should be noted that the applicant has requested approval for tazemetostat in an unselected patient population; that is, patients who may or may not have INI-1 loss. Therefore, FDA considers data from Cohort 6 to be especially relevant for considering the response rate that may be expected in such an unselected patient population.

Although the magnitude and duration of response are key to interpreting overall response rate, the FDA considers many factors when assessing whether an observed response rate is clinically meaningful and represents or may predict benefit to a patient. FDA considers benefits and risks of other therapies used to treat that disease: the clinical impact of tumor burden, the mechanism of

action of a drug as it relates to the biology of that tumor, the body of knowledge regarding the drug's effects in other settings, and the safety profile of the drug.

Due to possible differences in these factors, a response rate believed to be clinically meaningful in one disease may not be clinically meaningful in another disease. For the rest of the presentation, I will walk through the FDA's thinking regarding these factors as they relate to tazemetostat and epithelioid sarcoma.

There are no therapies specifically approved for patients with epithelioid sarcoma. Doxorubicin and pazopanib are approved for the broader population of patients with soft tissue sarcoma and are commonly administered to patients with epithelioid sarcoma. Doxorubicin was approved based on a response rate of 24 percent observed in 234 patients treated across 9 clinical centers. However, response criteria in that era generally defined a response as greater than 50 percent measurable decrease in tumor size. In contrast to

RECIST version 1.1, that defines a response as at least a 30 percent decrease in the sum of diameters of target lesions. Thus, the response rate used to support the approval of doxorubicin cannot be directly compared to that of tazemetostat.

Other factors that limit the comparability of the data in the two applications include lack of information regarding prior therapies in the doxorubicin dossier and differences in what constituted the efficacy of evaluable population between the two applications. For example, some of the studies used to support the doxorubicin approval excluded patients who received fewer than 2 doses of doxorubicin from the analysis, which deviates from the intent-to-treat statistical principles typically used today.

To try to get more information about response rates to doxorubicin in the modern era, FDA reviewed published studies from 2009 to 2019, which doxorubicin was the comparative arm for the treatment of patients with soft tissue sarcoma in the first-line setting. In these studies, the

response rates for doxorubicin ranged from 8 percent to 19 percent. There is insufficient data regarding the duration of response for both tazemetostat and doxorubicin to enable comparison of that endpoint.

Pazopanib was approved in 2012 for the treatment of patients with soft tissue sarcoma after chemotherapy, based on the results of a randomized placebo-controlled trial. Results demonstrate an improvement of PFS over placebo with an estimated hazard ratio of 0.35. The ORR was 4 percent in the pazopanib arm. In the subset of patients on Study EZH-202 that had received prior chemotherapy, tazemetostat yielded a response rate of 11 percent. While this point estimate is numerically higher than that of pazopanib, differences in underlying patient populations preclude direct comparison.

Because epithelioid sarcoma is a subset of soft tissue sarcoma and may be biologically distinct, FDA performed a review of the literature to look specifically at studies of doxorubicin and

pazopanib for the treatment of patients with epithelioid sarcoma. The available data was limited and consisted of small retrospective case studies. Both RECIST and WHO response criteria were used, and the eligibility criteria and resulting patient populations varied across the studies.

From the reported data, FDA is unable to conclude that patients with epithelioid sarcoma treated with standard therapies have different response rates than patients with other forms of soft tissue sarcoma. All of the analyses presented in the last two slides are limited by patient numbers, as well as measured and unmeasured differences in patient populations and differences in the frequency, timing, and method of response assessment.

The FDA considers the primary utility to be in demonstrating that all therapies used to treat epithelioid sarcoma have lower response rates and that tazemetostat does not appear to confer superior response rates compared to these agents,

based on available data.

Response rate and durability of response by themselves are infrequently considered a direct measure of clinical benefit by the FDA because it is difficult to determine whether the patient experiences any improvement in the way they feel or function, based on that data alone. However, there are some situations in which reduction of tumor burden can be clearly considered a direct measure of clinical benefit; for example, if responding tumors are less disfiguring or associated with improvements in patient-reported outcomes such as pain or ability to conduct activities of daily living.

As that type of data was not collected on EZH-202, FDA evaluated baseline tumor size as a potential proxy, with the idea that reduction in size of an exceptionally large tumor could provide some support for direct clinical benefit, however, 84 percent of the non-nodal target lesions were 5 centimeters or smaller in the longest diameter. Although the FDA acknowledges that not all of a

patient's tumor burden is accounted for by these measurements, unfortunately, the available data is insufficient to conclude that tazemetostat confers direct clinical benefit based on reduction of tumor size.

The last few years have given oncologists extensive experience with targeted therapies for cancer. Effective targeted therapies typically produce high response rates, demonstrating that the drug hits a target relevant for cancer cell survival. The applicant has described a hypothesis as to how tazemetostat may act in tumors with INI-1 loss that I would now broadly sketch.

EZH2 catalyzes histone H3, generally down-regulating transcription. INI-1 loss leads to abnormal activity or expression of INI-1 and a subsequent oncogenic dependence on EZH2. Tazemetostat inhibits EZH2, restoring transcriptional homeostasis. This is a fairly complex and indirect hypothesis.

The low response rate to tazemetostat in patients with INI-1 negative epithelioid sarcoma

could be because the target EZH-202 is not as relevant as had been thought to the disease biology, or it could be that the target is relevant but that inhibiting it in epithelioid sarcoma leads to effects that inhibit tumor cell growth rather than tumor cell death. This latter effect, which might be expected to yield durable, stable disease can only be assessed in a randomized-controlled trial.

The applicant recently released data at the American Society of Hematology meeting last week, showing that 69 percent of patients with follicular lymphoma, harboring a gain of function EZH mutation, responded to tazemetostat. The fact that this is 35 percent the response rate observed in patients without an EZH mutation suggests the relevance of the target to the biology of that particular cancer.

We do not have this type of confirmation for epithelioid sarcoma, as epithelioid sarcoma with retained INI-1 is exceedingly rare. However, we can say that the fact that 35 percent of the

patients with follicular lymphoma harboring wild-type EZH2 also responded to tazemetostat suggests that tazemetostat may have a more complex mechanism of action than is currently understood.

FDA based the primary evaluation for the safety of tazemetostat on data from Cohort 5. All patients in Cohort 5 experienced at least one treatment-emergent adverse event, with the most common being pain, fatigue, and gastrointestinal toxicities. Forty-eight percent of patients experienced at least one grade 3 or 4 adverse event, as listed here, and serious adverse events occurred in 37 percent of patients.

As Dr. Ward pointed out earlier this morning, it is important to remember that these adverse events are not all necessarily attributed to tazemetostat. On a single-arm trial, it is not possible to determine whether individual adverse events are present at a higher frequency in patients who receive tazemetostat than in those who do not, and thus establish a causal relationship.

Thirty-four percent of patients require dose

interruption for toxicity with hemorrhage and increased transaminases being the most common cause. One patient each experienced a dose reduction or discontinuation for toxicity. There were no deaths attributed to tazemetostat.

An identified risk, based on both nonclinical and clinical data, is the development of a secondary malignancy. Of the 686 adult patients with a solid tumor or hematologic malignancy who received tazemetostat at a dose of 800 milligrams twice daily, 5 patients developed AML or MDS. Across the entire development program for tazemetostat, which includes 822 adult and pediatric patients exposed to a range of tazemetostat doses, 6 patients developed a secondary malignancy. The incidence of secondary malignancy in patients exposed to tazemetostat is, thus, approximately 0.7 percent based on this data.

Secondary malignancies were diagnosed from 14 months to 4 years, from the times the patients started taking tazemetostat with a median time to onset of 27 months. Five of the patients had

received prior chemotherapies, which included drugs known to cause secondary malignancies. While none of the patients who developed secondary malignancies had a primary diagnosis of epithelioid sarcoma, FDA considers the risk to be applicable to all patients exposed to tazemetostat.

The exact mechanism by which tazemetostat can lead to secondary malignancies is unclear but appears to be linked to EZH2. EZH2 is expressed in a wide range of T-cell malignancies. EZH2 loss of function mutations have been identified in patients with hematologic malignancies, suggesting that the development of secondary malignancies may be an on-target effect of tazemetostat. In the nonclinical toxicology studies performed by the applicant, T-cell lymphoma with concurrent leukemia led to multiple early deaths in both adult and juvenile animals.

With limited clinical experience and lack of comparative data, FDA is concerned that activity observed in Cohorts 5 and 6 of Study EZH-202 may not be sufficient to establish the benefit of

tazemetostat in patients with epithelioid sarcoma. A key uncertainty regarding the application is whether the low response rate observed on EZH-202 will translate into a positive impact on survival or meaningful improvement in progression-free survival. While Epizyme has requested accelerated approval and is planning a confirmatory study of tazemetostat compared to doxorubicin alone in patients with the epithelioid sarcoma, enrollment into this trial has not yet begun.

Patients with epithelioid sarcoma make up a rare subset of patients with soft tissue sarcoma. Existing therapies are unsatisfactory, and we agree that effective drugs are needed for this patient population. Although a handful of patients on Study EZH-202 experienced quite durable responses, a point estimate of response rate of 11 to 15 percent means that it's possible that only a few of the patients with epithelioid sarcoma who take tazemetostat will see any kind of benefit from the drug.

Although tazemetostat has a different

mechanism of action compared to other drugs used for treating epithelioid sarcoma, inhibition of EZH2 may not be as relevant to the INI-1 loss that characterizes most epithelioid sarcoma tumors as has been postulated. While the drug appears to be very well tolerated, it is not without risks, which must be weighed against the potential benefits.

Finally, we did not have a large body of evidence of effectiveness of tazemetostat on survival endpoints in other cancers, which has sometimes been used by the FDA to support supplemental approvals of drugs and new tumor types on the basis of limited data.

The FDA asked the ODAC to discuss whether the evidence from Cohorts 5 and 6 of Study EZH-202 is sufficient to establish the benefit of tazemetostat in patients with epithelioid sarcoma. After this discussion, you will be asked to vote on whether the demonstrated benefit of tazemetostat outweighs the risk of the drug in the proposed indication. I thank you for your time. This concludes my comments.

Clarifying Questions to Presenters

DR. HOFFMAN: We'll now take clarifying questions for the presenters. Please remember to state your name for the record before you speak, and if you can, please direct your questions to a specific reviewer.

DR. HOTAKI: Just as a reminder, if you have a question, try to get my attention or Dr. Hoffman's attention. We'll be making a running list. If you have a follow-on to a theme and want to continue, put your card like this so we can note that it's part of a theme to move on. Thank you.

DR. HOFFMAN: I have a question for, I think, probably Dr. Agarwal or Dr. Demetri. With regard to tumor pain as an adverse event, obviously, I'm sure many of these patients have pain related to their cancers. Was there any correlation with response and having tumor pain? Was tumor pain a good sign, if you will?

DR. AGARWAL: I invite Dr. George Demetri.

DR. DEMETRI: George Demetri, Dana-Farber. If anything, our patients who were taking this

reported less tumor pain when they were on that period of time that was very durable for them. So we did not see any induction of pain, per se, by that. These patients had some exacerbations on and off, as we see with this disease. There did not seem to be a direct relation in any way to the study drug dosing.

DR. HOFFMAN: Dr. Cristofanilli?

DR. CRISTOFANILLI: I have two questions. One is in regard to slide 28. You were talking about 61 percent of patients have been exposed to prior therapy, and we heard about the efficacy of doxorubicin and pazopanib. Were these patients exposed to doxorubicin and pazopanib? Because in that case, it would be meaningful to see benefit in refractory patients to standard therapy.

The other one is regarding slide 44, where you mentioned 3 patients that had initial progress and has continued the drug and stayed somewhat stable. What type of therapy did they receive after they progressed?

DR. AGARWAL: Can you pull up the slide?

Here are the different types of prior therapies that we used in the ES population, the prior therapies, a breakdown. As you can see, the mix of different therapies, including doxorubicin, taxanes, ifosfamide, pazopanib, and other drugs that we used; so it was a mix of multiple drugs for patients who were exposed to prior therapy.

In terms of your second question -- and what's important to see in patients, and what we looked at, is the objective response rate in patients who were treatment naive and patients who had prior systemic therapy, and we didn't see much difference in terms of response rate.

In terms of answering your second question, what therapies they took after they progressed, that information we'll provide after the break.

DR. HOFFMAN: Dr. Sung?

DR. SUNG: Tony Sung from Duke; a follow-up question to that. Is there a difference in the response duration or the overall survival in patients who received the drug first line versus second line?

DR. AGARWAL: In looking at patients and response rate for patients who were treatment naive and patients who had systemic therapy, you see the response rate was very similar. In terms of duration of response, for the patients who were treatment naive, it does not available. In terms of prior systemic therapy, as you can expect, it was a little lower.

I would like to invite Dr. Schwartz to talk about the differences and the importance of the clinical significance of tazemetostat in epithelioid sarcoma.

DR. SCHWARTZ: Gary Schwartz, Columbia University. We know epithelioid sarcoma is, of course, a rare, highly aggressive tumor, which patients have very few therapeutic options. As an oncology community, we're not really convinced that standard chemotherapy has really any benefit in this disease. Response rates can vary in published data from 0 to 20 percent in soft tissue sarcomas.

Frankly, in my experience, I've never seen any patient that responds to standard chemotherapy,

whether it's doxorubicin based or pazopanib, in this disease. The data that we're comparing our response rates to, actually, for example, doxorubicin, is based on collected tumor types, not just epithelioid sarcoma 7.5 percent of doxorubicin, that's the most recent randomized, phase 2 study, and that was the doxorubicin control arm that led eventually to a registration study. That's our comparator, and the pazopanib, of course, 4 percent response rate based on a registration trial.

So looking at the historical data, as oncologists, we don't feel there's a role for standard chemotherapy in this disease. It's used, but its effectiveness is quite limited. When we see a patient with this type of cancer, we're looking for new therapies, clinical trials, or studies that we think have meaningful clinical benefit. In my experience, tazemetostat really achieves that goal in terms of response rate and stabilization of disease, which you don't ordinarily see with standard chemotherapies in the

treatment of this cancer.

DR. HOFFMAN: Dr. Klepin, you have a follow-up?

DR. KLEPIN: Yes. Heidi Klepin. I had a follow-up question to the conversation around symptoms and pain specifically. We didn't see any data on patient-reported outcomes or quality of life. Was anything collected on this trial that would be useful in that regard?

DR. AGARWAL: Unfortunately, we didn't collect the quality of life in this study, however, if you look at the safety profile of the drug in terms of -- we believe that tazemetostat is generally well tolerated. We had very low discontinuation rates and reductions. I would like to invite Dr. Demetri, who used this drug with patients, who would give you anecdotal improvement and about quality of life.

DR. DEMETRI: George Demetri, Dana-Farber. I do think the indirect answer to that -- we did not collect that. There were no quality-of-life forms that were given to patients. The indirect

measure was that when patients progressed, let's say, with a new lesion, an oligoclonal new lesion, we saw several patients whose primary target lesions, metastatic target lesions, were shrinking, and they were feeling better; back to the pain issue. Did we capture that? No. But did I see that? Yes.

I think the important thing is that's part of what we then say with this presentation of continuation of this treatment after RECIST defined progression, Because RECIST allows us to characterize those patients as progressing. Even if it's oligoclonal, even if it's one simple asymptomatic lesion, that patient gets kicked into the progression bin. But then we had the ability to talk to our patients and say -- several of the patients at Dana-Farber had had all available prior therapies and then some, so adriamycin, ifosfamide, gemcitabine, and a few other things as well, and they go on this.

We'd say, "Well, we could go back to something you've already had, or we could go to

palliative care, or we could continue this." And they said, "Look, this is doing fine by me. I'm tolerating it well. I actually felt better when I started it. That lesion you found, I don't feel it."

So that's the peculiarity of RECIST because you can be put into a progressive bin with a small lesion that's a new lesion, and I understand that. But this was what we were trying to express with the data as presented. So it's an indirect measure of some benefit. The patients were part of that shared decision making with us as well.

DR. HOFFMAN: Dr. Hawkins?

DR. HAWKINS: Just for clarification, probably from the FDA, the statement that we don't have studies that could compare prior treatment for epithelioid sarcoma and tazemetostat. The question is, natural history, isn't that well known enough to use the single-arm study, since we can't compare prior studies using chemotherapy to this new drug?

DR. WARD: This is Ashley Ward, FDA. I think what you're asking is do we have sufficient

information from published studies in epithelioid sarcoma to be able to use this study to compare to published studies?

DR. HAWKINS: I think the answer was no to that already. So my question is, is the natural history of this condition well known enough to use a single-arm study without a placebo because we can't really compare prior studies to this?

DR. WARD: Yes, I think that's a difficult question to answer.

DR. LEMERY: I think even if it's known, the question is whether the cohort of patients enrolled by Epizyme is going to match those patients. And it's such a small number of patients, I think it would be difficult to conclude, one way or the other, regarding any effects on survival, stable disease, and some of these other endpoints. Those would, I think, clearly need a randomized study to really understand the effects of the drug on those endpoints.

DR. PAZDUR: We have used single-arm studies for many approvals, and we look at response rates.

And the reason why we look at response rates is because that response is due to the drug alone; it is not due to the natural history of the disease.

As Steve pointed out, we don't look at other endpoints such as progression-free survival, overall survival, time-to-event endpoints. Those do require a comparison. But response rates are a special endpoint in oncology. So given the information that we have here, we have to have a discussion whether this observed response rate is of potential benefit to patients.

DR. HAWKINS: Thank you.

Just a query for the applicant's plans to -- how long do you think it will take for the enrollment with your planned study of tazemetostat and doxorubicin in the future? Again, the enrollment hasn't started yet, we're told. How long do you speculate it will take for this study?

DR. AGARWAL: So the phase 2 study, we have already the site open, and we basically are initiating the study. As I was mentioning, it's a rare tumor. It's about 125 cases a year. It's

difficult to enroll the study. We are initiating and we are very committed. I think in terms of enrollment, what we're projecting is about six and a half years for enrollment, and then follow-up of about a year.

Basically, we are opening all the sites and putting U.S. and ex-U.S., and have almost 130 sites for study and are committed to study that and provide information. But it's a rare tumor. It's very difficult to enroll this tumor because, altogether, with 2 cohorts, we have about 106 patients.

DR. PAZDUR: You don't have the dose, the combination yet; do you?

DR. AGARWAL: Thank you, Dr. Pazdur. So we actually are starting that study. We have a patient in screening, and we'll be enrolling, and we'll possibly have those within a few months.

DR. PAZDUR: So at the present time, we do not have the dose of this.

DR. AGARWAL: No.

DR. PAZDUR: Could I follow up on this --

DR. HOFFMAN: Yes.

DR. PAZDUR: -- if I may? Could you tell us a little bit about the study? I think it's important for us to have a discussion of this study also, and that is in regards to the effect size that you're planning on demonstrating, because obviously you have planned 130 patients in a randomized study, which is a relatively small study; let's be quite honest with you. And usually small studies look at, unrealistic many times, effect size.

So the effect size that you're postulating in this study is what, and how was that determined?

DR. AGARWAL: We're basically using an effect size with a control arm of 8 months of PFS benefit in tazemetostat, about 15 months with 81 PFS events, with an 80 percent power, based on the olara trial and the recent data on front line. That study is proposed in a front-line setting. That's the proposal we discussed with FDA.

DR. PAZDUR: So the difference that you're looking at is what?

DR. AGARWAL: It's from 15 to 8 months; from 8 months to 15.

DR. PAZDUR: So 7 months, basically. How was that derived? Because, here again, you have a drug that has about less than a 15 percent response rate, and to think that you're going to have a very impressive effect on progression-free survival.

DR. AGARWAL: So we basically looked at PFS as an endpoint, and based on the data that we have preclinically, we believe that there may be synergy in terms of combining the two drugs, doxorubicin and pazopanib. We used the olara study as a comparator, and the hypothesis will be able to show that benefit.

I think in terms of looking at the data, we'd be open to discussing with the agency about if we have to look at the different effect size, or even an endpoint, based on the post-progression benefit that we are seeing in our phase 2 study and possibly survival as an endpoint.

DR. PAZDUR: Another question that I have -- and here again, I'd like to have some

discussion on this protocol -- the issue is, obviously, this is a frontline study, and the drug would be approved in a more refractory population. But in general, in oncology patients, a drug with refractory disease usually has activity in an earlier stage of disease, if not better activity. So you'd be asking patients, basically, to go on an approved FDA drug, basically, or not to go on an approved FDA drug facing a life-threatening disease here.

Do you think that this study really has equipoise that patients would go on it? For example, I'm thinking about a patient facing a disease, a life-threatening disease here, and if the FDA approved this drug, we'd be asking patients to go on standard therapy versus the new drug, a combination with the standard therapy. Would patients actually go on this study?

DR. AGARWAL: Sure. I would like to invite Dr. Demetri, who is one of the investigators possibly for this study and who's participating. He can give his view.

DR. DEMETRI: George Demetri, Dana-Farber. I think that's an important element of what went into this, the issue that you're not seeing -- and I wonder if the preclinical data that Dr. Agarwal referred to might be useful for people to know, that the idea that there are some preclinical data that support some additive, if not synergistic, benefits.

I'll put this up here on the slide. Here we see a percent of vehicle control with this ES cell line, INI-1 deficient, where tazemetostat at that dose, 1.3 micromolar, decreases the tumor cell count. Doxorubicin similarly decreases tumor cell counts, but the combination is more than additive.

What I'd like to emphasize is if that indeed is the case, there are patients who may choose to go for that extra benefit of combination therapy, especially patients who are symptomatic with their disease. If there are others who choose not to do that, that's a discussion we have. I would personally have no problem with the equipoise there because some of our patients are willing to say I

have this life threatening disease; I want the most aggressive therapy possible. Other patients will say I'd like the least toxic therapy possible.

I also think that going ex-U.S., outside the United States, will be an issue here because there are many patients who are certainly suffering from this disease outside of the United States, and this trial will aim to find them as well and offer them this. Typically, the United States has access to these drugs sooner than other parts of the world -- thank you for that -- and I think that will be something that other parts of the world will be able to participate in so that we can, as we have a global sarcoma community, function in that way and get this study done.

DR. PAZDUR: Just to follow up on that statement, could you share with us any discussions that you've had with other regulatory agencies regarding this application, specifically the EMA and what your plans are with them?

DR. AGARWAL: So we haven't for now had any discussion with the EMA in terms of any

submissions. Currently, we don't have plans for use submission. We will be planning to do this study in Europe, in all the countries, pretty much where we actually use.

DR. PAZDUR: Is there any reason why you haven't discussed this application?

DR. AGARWAL: I think --

DR. PAZDUR: It's a huge market, obviously. Most companies do pursue global registration programs.

DR. AGARWAL: I think, Dr. Pazdur, as you know, we were thinking about the DS [ph], and we also have an FLND that we just are planning to file as well. So being a small company, we were focusing our -- and also wanted to align with FDA first before we think about any opportunity.

DR. PAZDUR: One of the reasons I'm bringing this up is having been in this chair for 20 years, I've heard many companies say that they're going to be doing trials. One of the problems that we've had with the accelerated approval program is many times these trials have not been done if they are

not initiated. They're supposed to be done with due diligence. And here again, we don't even have a dose here of the drug. We have to have that under consideration.

One other regulatory issue that I'd like to pursue with you is how many single-patient INDs have you had with this drug?

DR. AGARWAL: We have an expanded access program right now.

DR. PAZDUR: How many single-patient INDs?

DR. AGARWAL: Do you have that number? We can get that after the break.

DR. PAZDUR: And you have submitted a treatment protocol --

DR. AGARWAL: That's right.

DR. PAZDUR: -- to this application?

DR. AGARWAL: That's right.

DR. PAZDUR: If this drug is not approved, do you plan on pursuing that treatment protocol also?

DR. AGARWAL: We have the expanded access program. It was in between the drug approval as

well as the application. It is also open for other indications as well, but as you know, we want to be able to get this drug to the patient as quickly as possible, at the next expanded access program. I would like to invite Dr. Demetri to talk about some of the --

DR. PAZDUR: Well, could you please answer my question? Would you continue the treatment protocol for this disease if this drug is not approved?

DR. AGARWAL: We are committed to provide the drug to the patients.

DR. PAZDUR: Thank you.

DR. HOFFMAN: We have a series of follow-ups before we get to additional questions. Dr. Cheng?

DR. CHENG: Actually, I was going to follow up with Dr. Schwartz rather than talk about Dr. Pazdur's questions about the follow-up studies. I saw Dr. Schwartz's comment that the treatments for patients with ES are more resistant than soft tissue sarcoma. I also saw that the FDA provided, I think it was slide number 11, that their

viewpoint, it was similar. So I just wanted to understand that a little bit more, if there is a reconciliation.

DR. AGARWAL: Dr. Schwartz?

DR. SCHWARTZ: Gary Schwartz, Columbia University. These are historical data sets of small sample sizes that are very difficult to interpret. You can see the large range of responses seen here with rates as low as zero percent and with aggressive chemotherapy as high as 22 percent. Again, I think looking at the total data set, it's hard to know exactly where epithelioid sarcoma fits into this data set.

I can show you a patient, actually, who I think has had a profound benefit just to give you a sense of what it looks like in a patient. Can I have the first slide?

Here's a patient. Actually, it's interesting case history. I know it's anecdotal, but I want to share with you the resistance of this patient. This is a patient with an epithelioid sarcoma. Here's a big, right anterior chest wall

mass under the right breast. The patient, actually who had failed her epirubicin ifosfamide, entered the second based chemotherapy, had failed ifosfamide single agent, had failed gem-docetaxel, and at this point was put on gem-vinorelbine. So this is a fourth-line therapy for a large tumor mass, and a patient progressed at 2.5 months.

The patient started tazemetostat. Here's the baseline study of progression. You can see that mass has now dramatically increased in size; then what happened was here's the target lesion on this patient who's on the clinical study, and at 3 months has a partial response; and at 25 months, that mass continues to decrease; a sustained partial response; and unfortunately at 30 months, they developed a new lesion right next to them, or more centrally, and that was RECIST POD.

So this is the problem we face in this disease. It's a disease we can see dominant masses that respond despite failure on prior chemotherapy. Also, it's a disease where you have multiple small metastatic lesions that line the pleura, so it's

with profound pleural effusion and hemoptysis, and multiple sites of soft tissue disease.

So this is a disease that, in our experience, tends to be highly refractory prior to chemotherapy in contrast to other soft tissue sarcomas, which by the way are also generally chemotherapy refractory. There are very few sensitive patients who respond well to chemotherapy in this disease, and no data in any randomized study that patients have a prolonged survival benefit beyond doxorubicin alone, despite multiple attempts to show and recent negative data from studies showing no benefit beyond dox.

So this is a disease that we cannot assume that chemotherapy has much effect as even in non-epithelioid sarcomas, let alone epithelioid sarcomas, which in our experience I think is one of the most chemotherapy-resistant resistant tumors. But I want to show this example of a patient, multiple lines; fail, fail, fail; comes on trial; and I think you can't deny that's a rather significant radiological and clinical benefit to

the patient at chest wall pain.

DR. HOFFMAN: Dr. Uldrick?

DR. ULDRICK: Yes. I have a follow-up question regarding the study design for the randomized-controlled study. One of the hard parts about understanding this disease is we really don't know the natural history of the disease, including the natural history of response to doxorubicin. I was just wondering if you could comment on the control arm as to why you had chosen doxorubicin as a control arm, and why there's not an arm looking just at tazemetostat if you believe that's superior to doxorubicin.

DR. AGARWAL: The rationale we used, combined with doxorubicin, is based on the preclinical mouse models and the synergy of the data that we saw. I would like to invite Dr. Penebre to talk about this data and what synergy we observed.

DR. PENEBRE: Elayne Penebre, preclinical research at Epizyme, studying the biology of EZH2 for over five years. I'd like to start by showing

the preclinical data that Epizyme performed in an INI-1 deficient epithelioid sarcoma cell line treated with tazemetostat alone, as you can see on the left, doxorubicin alone in the middle, and the two agents combined.

The Y-axis represents percent of control in cell counts, and what you can see are the two agents exhibiting antiproliferative effects alone. However, when the two agents are combined on the right, you can see synergy observed, and this supports using doxorubicin and tazemetostat as support for our phase 3 confirmatory trial.

DR. ULDRICK: I guess my question was why you chose doxorubicin as the control arm.

DR. AGARWAL: Yes. In the frontline setting, I would like to invite Dr. Demetri about the frontline setting and use of chemotherapy.

DR. DEMETRI: George Demetri, Dana-Farber. The world standard front line, right or wrong, is doxorubicin, so I think to have a patient with metastatic, life-threatening sarcoma not receive the standard frontline therapy would have been

unacceptable to patients and physicians.

We've heard a lot about these papers. I hate to do this, but I will say this. The RECIST -- if you could pull up those papers, Frezza and all that, the retrospective literature, I want to emphasize one problem that I'm shocked that no reviewer has actually pointed out in these papers. You see, it was said to be by RECIST. Let me just pass on those.

We shared the same papers, the ones on the bottom here, these four papers. Jones and Frezza, particularly in methodology, say RECIST defined progression. If you really look at that, those were retrospective case series without independent central radiology reviews. When I've done that sort of thing, you hire an independent person, have them pick target lesions at baseline, and then prospectively go forward in the series.

In this, investigators retrospectively were asked to assess by RECIST. So retrospective review of RECIST, I want to just insert a little question about the quality of the evidence we're dealing

with. The fact is, as you've heard, our experience doesn't necessarily match up with this. We're quibbling at the edge because 20 percent response rate is quite low, but I would even question the 20 percent response rate because these retrospective reviews do not involve prospective RECIST-defined measurements that are applied in properly conducted clinical trials such as this one. So I just wanted to point that out.

So your point about using doxorubicin rather than anything else is simply the standard worldwide that everybody could agree on in a worldwide study.

DR. HOFFMAN: Dr. Cheng?

DR. CHENG: Thank you, Dr. Demetri. Can I just ask a follow-up if I may? Can you comment on the duration of response as to what is expected with standard of care as well? I saw that pazopanib actually had a response duration of I think 9 months, while that table showed less than 2 months; and yours is 16.4, although I understand the FDA's concern about small numbers; but just comment on what the expected duration of response

is to standard.

DR. AGARWAL: Can you open the duration of response curves, please?

DR. DEMETRI: George Demetri, Dana-Farber.

DR. AGARWAL: No, the one with the historical slides.

DR. DEMETRI: I think this is part of why our community feels strongly about the drug, because these exceptional responders are real. The people who have stability of disease, the ones who have gotten those sorts of responders, that patient that Dr. Schwartz showed who had 30 months of disease shrinkage and continued duration of response for 30 months, I've never seen with an epithelioid sarcoma; and that patient had prior chemotherapy failure, and those prior chemotherapies did not induce this kind of response.

So when you're dealing with a rare disease, if you have a sensitive subset of patients -- and I will be honest with you; we don't know who that sensitive subset is for chemotherapy. We don't

know who that sensitive subset for this drug either, but clearly, it exists. And I think the issue here is that if there's a long duration of response with a drug that's well tolerated in a subset of patients who have an otherwise uniformly fatal disease in a short period of time, that's the question. How can we assess that risk and benefit?

I think as somebody who treats these patients, we have not seen that long duration of disease. The fact that the patients entering this study had a median time on prior therapy of 2.4 months; most of the reasons people come off prior therapies with a life-threatening disease, the therapy is not working. So I want to just point that out.

DR. AGARWAL: I think just going back to Dr. Pazdur's question, it's important to highlight that for this cohort, not only did we show the response rate, which may be similar as Dr. Demetri was talking about, but what's important is the duration of response that we just talked about, and also the fact -- I understand the caveat to a

single-arm study -- that we did see a longer median survival and a durable stable disease, which we believe maybe correlating with survival, especially in sarcoma.

Additionally, just with the epigenetic mechanism, what we see is patients are benefiting beyond progression, RECIST progression. As you can see, there are some patients who had a decrease in target lesions, and the drug is well tolerated.

DR. HOFFMAN: Dr. Cristofanilli, a follow-up?

DR. CRISTOFANILLI: This is a follow-up regarding the prospective randomized study. Is there any concern that combining this drug with doxorubicin will increase leukemia or any possible bone marrow long-term effect?

DR. AGARWAL: In terms of the phase 3 study, we believe that we didn't see any secondary malignancies in the ES population, however, we will be, to your point, monitoring these patients very closely. Doxorubicin will be given for 6 cycles, and then it will be stopped and then maintained on

tazemetostat. We also are placing safety monitoring committees to ensure that we are watching these patients very closely.

DR. HOFFMAN: Dr. Sung?

DR. SUNG: Following up on that discussion as well, one question for Dr. Agarwal and one question for Dr. Pazdur.

Dr. Agarwal, in the previous slide, you highlighted the fact that on this current trial, there were patients who progressed by RECIST criteria but then still seemed to derive benefit. In addition, you highlighted a benefit of overall survival. Why are you powering the study to PFS as opposed to overall survival?

DR. AGARWAL: So in terms of the study design, I think this is a benefit that we've seen post-progression, and we believe that it's really real and it's clinically meaningful. We will be open to talking to the agency to change the endpoint to survival because we believe that may be a better surrogate of what we're observing in our phase 2 study.

DR. SUNG: Then my question for Dr. Pazdur is, you mentioned sometimes when drugs are approved, subsequent studies do not enroll rapidly or are not completed. Are there mechanisms by which the FDA can monitor the real-world usage of drugs that go through accelerated approval to gather more data, to ensure that the results of small trials are carried out?

I want to highlight, for example, the pazopanib data. In one study, there was a 27 percent response rate; in another study, there was a 0 percent response rate. I think with such small numbers, it's important to capture that real-world experience.

DR. PAZDUR: Well, let me just address the survival issue. This is a rare disease, and to do a survival study would require large numbers of patients, potentially. I think that that would be a very difficult endpoint to establish in this disease, although it's a preferential endpoint; but here again, you would even need more numbers. One of the things that is causing me some heartburn

here is the issue that this trial will take 7-8 years, projected even at this time, to be done, so to speak. So to look at a survival study, it might be unrealistic to do, just to put that elephant to rest, so to speak.

The issue about real-world data, that's an area of emerging data, emerging science. We could take a look at this. We know and we have ways of looking at drug utilization, that's for sure, but to get actual endpoints is something I would term as an evolving area for the agency to look at. Here again, one would have to take a look at how well-controlled response rates were measured in a real-world situation and how one could accurately capture survival in some of these data banks, et cetera.

So this is not something that I would preclude, however, on the other hand, I would not promise that this would provide us that information.

DR. HOFFMAN: Dr. Klepin?

DR. KLEPIN: Yes. This is also a follow-up

on the conversation around how potential approval of the drug and the indication here might affect whether or not the subsequent phase 3 trial can be conducted, which I think is a relevant conversation. The question is actually very basic for the applicant. It's around the specific context of the indication that you're seeking.

So are you seeking approval in all lines of therapy; so first-line approval in this indication? Most of the patients that were in the study cohorts presented have received prior lines of therapy, so it seems as though they were second line and beyond. That approval line could certainly be a factor in influencing whether or not a subsequent phase 3 trial in a first line could be conducted most efficiently.

DR. AGARWAL: Yes. Since the study included both treatment naive locally and patients who are pretreated with systemic therapy, the indication is for all patients. In terms of frontline therapy, the indication right now is for all patient populations because we saw benefit in both the

populations in the phase 2 cohort, but I understand your point in terms of the phase 3 study.

I think the important thing that I do want to point out for the phase 3 study, I understand Dr. Pazdur's comment completely, but I do want to say that the company is very committed to start the trial. Of course the challenge is the indication and the small patient numbers. But we basically are planning, and we have already initiated the sites, and we are very committed to complete the study as a company.

DR. HOFFMAN: Dr. Lemery?

DR. LEMERY: I just want to comment on some of the previous things that have been said I think on the sponsor side. As someone who was diagnosed with cancer myself about a year ago, to see some of these claims about improved survival, 19 months of survival, and longer duration of response, based on some of the single-arm data, we have small numbers of patients. Even in the sponsor's own data for survival, looking at comparison to a natural history study in the second line setting, survival

is about the same in those patients. So any improvement in survival would be in the first line, based on a very, very small number of patients with their drug.

I think reasonable people can have a discussion about an effect on response and whether that's important to patients, and I think that's important. But I think as someone who's gone through this myself, to see some of these claims being bandied about on single-arm data, really, I know strike up a chord in me, and it frustrates me as a patient.

I think we do need to have these discussions about the effects observed with the drug, but I think we need to be honest about what the effects are and what they're not because, ultimately, this is a public presentation, patients are hearing this, and they need to know what the true effects are likely to be if they receive a drug, both good and bad.

DR. HOFFMAN: Dr. Halabi?

DR. HALABI: Thank you. I had a lot of

similar questions that were answered, but I would like to go back to the prior systemic therapy and among those 38 patients who received at least one, if you can display the prior therapies, systemic therapies, that the patients received, if you can display that slide?

DR. AGARWAL: Display the slide with the kind of prior systemic therapy.

DR. HALABI: Because I find it quite remarkable that 4 out of the 5 patients who had developed malignancies received doxorubicin. I know this is the standard of therapy, so this is why I was also questioning the combination of the drug with doxorubicin in your phase 3 trial. I think you're showing the data again, and 26 out of the 62 patients had doxorubicin.

DR. AGARWAL: Just to clarify in terms of secondary malignancies, we saw that in lymphoma; we didn't see anything in the primary ES population. I want to provide Dr. Zeidan, who actually reviewed these cases himself, to provide a view of our secondary malignancies.

DR. ZEIDAN: Thank you. Amer Zeidan, associate professor of medicine at Yale University. I specialize in the management of myeloid malignancies, and I have actually a special interest in therapy-related AML and MDS. I have reviewed the 5 cases that were shown for myeloid malignancies, as you can see here, and I think you pointed out a very good confounding problem that often happens in the assessment of secondary malignancies that we often see, is that all of those 5 patients have received either chemotherapy radiation or both.

As you can see, 4 of them were within the lymphoma cohort, none of them were within the last cohort. The 5 patients who are males are older than 55, which are demographic segments that are enriched for the development of myeloid neoplasms, and some of the patients did have some dysplasia or blood count abnormalities that suggest some ongoing, potentially, bone marrow issue at the time of entry into the study. Because of all of these reasons, I think it's difficult to ascertain,

basically, the relationship to myeloid malignancies in this cohort.

I would go to other points I think important to consider. One, each time we think about secondary myeloid malignancies, you have to think about their risk. We are looking at less than 1 percent, or 1 percent, and that's very similar to what you see, for example, within the lymphoma cohort in heavily treated patients with lymphomas who receive multiple lines of treatments and also with patients who got doxorubicin.

I think the third point to consider is always the context of therapy. I think the issue of secondary malignancies, in my view, is much more relevant for patients who are being treated with curative, intent type of therapies, where the patients are expected to live many years. Unfortunately, in malignancies where the survival is in the order of a year or less than a year and those myeloid malignancies can take some time to go, the unfortunate reality is the vast majority of patients die from their underlying disease rather

than secondary malignancies, so I think understanding the context is very important.

However, I think you bring up a good point, and I think the company's planning to initiate monitoring programs for the development of myeloid malignancies that are going to be in the drug label. I think there should be a very robust postmarketing surveillance type of approach if the drug is approved. Thank you.

DR. HALABI: Thank you. The next question is I know there were only 8 patients who progressed in the trial, but I haven't seen a PFS curve. Can the sponsor show us the Kaplan-Meier curve by PFS since this is going to be the basis for your phase 3 trial, the 301 trial?

DR. AGARWAL: Here is the PFS curve, the progression-free survival Kaplan-Meier curve that we saw in the ES population. Just to remind, these patients are the metastatic patient population, mainly a very sick population that we enrolled. I would actually like to invite Dr. Demetri to talk about the context of PFS and what was observed with

pazopanib to provide this context.

DR. DEMETRI: George Demetri, Dana-Farber, again. The PFS data are as they are here. What is particularly notable is potentially the tail here; again, the idea that there's a subset of some patients who have prolonged stable, non-progressive disease. I understand all the complexities we've raised today, and I appreciate that.

Remember, in the confirmatory study, PFS is in the context of a doxorubicin addition, so the question of the combination results and what could be expected with doxorubicin. The one nice thing about the confirmatory study is that there have been several large international studies now that have a control arm with doxorubicin, so we have very accurate estimates about what could be expected with a sarcoma population in the control arm, not with an epithelioid sarcoma population per se. That's about the best we can do with that.

DR. HALABI: I have one final question. Also, as a statistician, I'm struggling to understand how some patients have progressed and

then they had experienced PR. Can the sponsor comment on that?

DR. AGARWAL: Yes. Basically, in the protocol, we had allowed patients to continue beyond progression if the investigator believed that there was clinical benefit in consultation with the patient; so if they had RECIST progression, they would continue on therapy.

Here are the 17 patients in Cohort 5. As you can see, these patients and physicians, if they had a new lesion or small lesion, they actually continued on therapy post-progression because they believed that there was benefit. This is post-RECIST progression, so they continued on therapy. Some of the patients actually continued for a long time and had a clinical benefit.

I would like to invite Dr. Demetri because he actually had a couple of patients who went beyond progression, in this patient, and the benefit he observed in that patient population.

DR. DEMETRI: George Demetri. I actually would like to put this slide up, which are all of

those patients, to show the investigators who did this continuation of therapy after RECIST defined progression, what were their reasons. In our patients at Dana-Farber, it was a patient whose primary lesions that were the target lesions were shrinking -- something else was not viewed as clinically significant -- the issues of tolerability, slower disease progression, like patient 8, and the patient was asymptomatic and feeling well on the treatment. So there are several reasons that physicians and patients together decided to continue.

Let me also clarify one thing. The sponsor is not trying to claim partial response. Once you're progressed, you're progressed. They were trying to point out that the target lesions shrank to the point of what would have been a partial response had a new lesion not showed up. So I think that's important, that we're dealing with the complexities of RECIST's prospective definition and picking target lesions.

Let me also emphasize this. The target

lesions that are measured are a subset of the total body burden of disease. That's another important element as we think about the clinical use of RECIST. It's good, it's probably the best we've got, but it's this peculiarity of that to help understand this.

DR. AGARWAL: I do want to invite Dr. Schwartz on providing his feedback about the duration of response in this ES population; what you saw with tazemetostat and why it is important in this aggressive tumor type and unmet need.

DR. SCHWARTZ: Gary Schwartz, Columbia University. Yes, we did see patients with clinical benefit on the trial with prolonged disease stabilization. This is the overall mean duration of response in this patient population, and you can see the median duration response is 69.7 weeks, which we would think is being a clinically significant outcome in this patient population.

DR. HOFFMAN: Dr. Hinrichs?

DR. HINRICHS: I wanted to go back to the primary data set a little and ask about stable

disease. Of course, the applicant is using stable disease as a metric for the activity of the drug, and it's, of course, a highly problematic metric. The FDA doesn't accept it as a metric, and for good reason.

Having said that, RECIST, which of course defines the stable disease category, which we've just discussed as probably our best metric, is also a highly limited metric. The more I try to deal with it, and the more I see clinically and how it ends up being matched up and measured by RECIST, the more I realize how limited that tool is.

The question that I have for the applicant is, when we're looking at stable disease, one way to get a sense of whether that represents a change in the disease course would be how much the patients were progressing before they were treated, and Dr. Schwartz made the comment, I believe, that the majority of the patients were progressing at the time that they were treated.

Can you give us more detail about how many patients were progressing and how quickly they

progressed? Also, knowing that this would be a problematic metric, do you have raw data that plots the rate of the patient's progression prior to starting on the drug?

DR. AGARWAL: In terms of the patient population, as you can see, the majority of these patients were stage 3-4; 95 percent of the patients had progressive disease prior to study entry; and the median time from progression, from the last therapy, was about 1.4 months. Importantly, we also looked at the duration of treatment on prior therapy just before they came on our study, and that was 2.4 months median, so it was a heavily pretreated population.

I do want to invite Dr. Schwartz to talk about this progressive disease and how they are different from a locally advanced patient population in terms of the course of the disease, and looking at this patient population.

DR. HINRICHS: Before you move on to that, can I just follow up on what you just said? The progressive disease prior to entry in the study, I

see that was 95 percent. How is progressive disease defined?

DR. AGARWAL: Yes. In the study, basically, it was either RECIST or clinical progression, and that was entered in the study the date of progression for the last therapy.

DR. HINRICHS: When you say clinical progression, how is that defined?

DR. AGARWAL: It was at the investigator's discretion.

DR. HOFFMAN: Dr. Ward?

DR. WARD: Ashley Ward, FDA. I just wanted to follow up to Dr. Hinrichs' question about stable disease. Could you go to FDA's slide 29? We recognize that RECIST does have some limitations, but there are quite a few reasons why the FDA does not consider stable disease and efficacy assessments. As we mentioned previously, primarily this is because while the response could be attributed directly to a treatment, stable disease can occur with and without treatment. The percentage of patients who experience stable

disease at any given time point depends on the natural history of the disease.

Could you go to slide 30? Just as an example, here's a randomized study of pazopanib versus placebo. If you look on the placebo arm, 38 percent of those patients had a best response of stable disease. Placebo doesn't have any activity in the tumor. So this is just an example of why the FDA does not consider stable disease to be relevant in a single-arm study. Thank you.

DR. AGARWAL: Can I invite Dr. Schwartz to provide some insight in epithelioid sarcoma and stable disease?

DR. SCHWARTZ: Yes, I get the point of the FDA, but this is sarcoma, and this is epithelioid sarcoma, and this is a bad, bad disease. I cannot reinforce the point, as a sarcoma specialist, that we do not see stable disease in this population. Everybody on the study had progression of their disease. We start treatment, we have responses, and then we have stabilization of disease. I don't know how to attribute that to the natural history

of the cancer. I only see the patient starts the drug, progressing disease, and now the disease stops to grow.

This is a bad cancer. We have to separate this from other types of sarcoma. I think that's one of the things we have to address. This is not your typical sarcoma. This is epithelioid sarcoma, 125 patients a year, people dying every single day from progressive disease. It does start as small-volume disease, absolutely, but by the time it comes to clinical trial, these patients have aggressive, progressive, and rapidly progressive disease.

So I don't know how to explain stable disease by the natural history of this cancer. I am sympathetic to this outcome, but I do not think that conclusion applies to this patient population, as a sarcoma specialist in this cancer.

DR. HOFFMAN: The last question before we take a break --

DR. HINRICHS: Can I follow up on that; just kind of following the line of questioning that I

started?

It's clear that it's the impression of the physicians who are presenting from the applicant today that they think that the stable disease we're seeing is a change in the course of the disease from what it was doing naturally. What I'm asking for is if you have data to support that.

DR. AGARWAL: Can you open the spider plot, for all patients, the spaghetti plot? Here, you can see in the spider plot, as you can see it below, this is basically a spaghetti plot showing --

DR. HINRICHS: I'm sorry. I want to interrupt you again because this is not what I'm asking. What I'm asking for is what was going on to the left of zero?

DR. AGARWAL: I see. In terms of prior therapy, you mean, just to clarify?

DR. HINRICHS: In terms of the disease progression before you supposedly altered the course of the disease by administering a drug? I'm asking you for that data.

DR. AGARWAL: I can provide that data after the break. We'll provide that data after the break.

DR. HOFFMAN: Ms. Webb?

MS. WEBB: Thank you. Kimberly Webb. I'm the patient caregiver. I'm the mom. I had a question about the pazopanib that you showed. Was that epithelioid sarcoma?

DR. WARD: Ashley Ward, FDA. No, that was all soft tissue sarcoma.

MS. WEBB: Okay. Then I'm going to say that I'm anecdotal, but I do have, like I said, over a thousand members on our page, so I'm in communication with the people that are actually inflicted with this horrific disease. And I'll tell you that I agree with Dr. --

DR. AGARWAL: Schwartz --

MS. WEBB: -- Schwartz completely. That's what we see when we're out there in the trenches, that it doesn't stop. We go month to month, or 3 months, to our scans, praying every day that we hear that you're clear or you're stable; that it

hasn't grown. So the stable disease is exactly like what Dr. Schwartz is referring to. If it's not growing and that's stable, then it really does make a difference for our world. So it's unfortunate that the FDA is not able to recognize the stable disease part.

DR. AGARWAL: And I think it's important to highlight as well the durability that we're observing along with the survival benefit.

MS. WEBB: I actually have, over and over and over, talking about tazemetostat from one of our member's son.

"No side effects. Been on it for seven months. Tumor's stable." Another one. "My son taking it as well as part of a trial since January 2018 with no side effects."

Here's another one. "I'm on 800 milligrams, twice a day, 12 hours apart. If I take it with food, there's no side effects." "I have a little bit of fatigue" -- here's another person -- "but minimal."

Another one. "My son Tyler took it

6 months, stable scans." "I'm just trying to get on this. Is there any way I can get this drug?" That's from another member.

As far as what Dr. Lemery was saying, one part about this drug is that we're able to actually function, so we're seeing people that are actually able to go out and do things. We're not just in our death beds, right? That's got to mean something, too, I would think, but that's not on these slides. These are kids. A lot of the ones that I said, they're 18, 19, 22, 30 years old.

DR. HOFFMAN: Last clarifying question from Dr. Riedel, and then we'll take a break.

DR. RIEDEL: Hi. Rich Riedel from Duke. This is less of a question and more of a comment. I would just say that as a medical oncologist who sees sarcoma patients that are not representing the sponsor, in my opinion, I will agree with everything that the medical oncologists who have spoken to date have said with respect to the natural history of this disease. While we may not have data -- although I'm not particularly aware of

data that we can pull that speaks to this -- this is an extraordinarily aggressive disease that does not respond to standard therapy. Thank you.

DR. HOFFMAN: We'll now take a 13-minute break. I'll remind the panel members to please remember there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We'll resume at 10:30. Thank you.

(Whereupon, at 10:17 a.m., a recess was taken.)

Open Public Hearing

DR. HOFFMAN: Let's reconvene, please.

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 open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral

statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, it's direct competitors.

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open

way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MR. NELSON: Good morning. My name is Jeff Nelson, and in March of 2011, at 44 years old, while drying off after my morning shower, I felt a strange, painless lump on my left butt cheek, that would later be diagnosed as peritoneal proximal variant epithelioid sarcoma. That's how my cancer journey began. Eight and a half years and 2800 miles from home, I find myself in Maryland.

Even though long trips are difficult for me, I think that speaking to you about my experience outweighs my pain and suffering. Epizyme has paid my travel expenses and enabled me to speak at this meeting, and I want you all to know that I

100 percent believe, based on my experience, that tazemetostat should be approved as a treatment for epithelioid sarcoma.

In 2011, I had never heard of epithelioid sarcoma, and neither had my doctor, my surgeon, and not even the local pathology labs. It's understandable when you realize that epithelioid sarcoma accounts for only 1 percent of soft tissue sarcomas, and the much more aggressive peritoneal proximal variant accounts for less than one-third of those.

Over the past 8 and a half years, or 8-plus years, of fighting this disease, I've had 4 surgeries, 73 rounds of radiation therapy, and approximately 28 rounds of traditional chemotherapy; and by traditional chemotherapy, I mean the lose your hair, every hair on your body, and make you sicker than your worst nightmare sick chemotherapy.

In 2011, following rounds 3, 4, and 5 of ifosfamide, doxorubicin, or chemotherapy, I was hospitalized for a total of 20 days for

neutropenia, and I contracted C. diff twice, and that was enough. I canceled round 6 and 7 for fear of not surviving the chemo. I've needed multiple transfusions. I've had hand-foot syndrome, where the palms of your hands and the soles of your feet burn like a terrible sunburn, then peel, and then repeat; a lower bowel obstruction that I wouldn't wish on my worst enemy; and all of these were side effects during traditional chemotherapy.

From the combination of surgeries, radiation, and chemo, I now have permanent neuropathy in both legs and lipidemia in my right leg and groin, which has led to hip and back pain when I walk, stand, or sit for long periods of time.

In early 2016, I began to hear about a clinical trial for epithelioid sarcoma patients using a drug called tazemetostat. I searched the internet and ES groups for information about tazemetostat, and what I read was really exciting. It was an oral medication -- no more needles -- that I could take at home -- no more

expensive travel and hotel stays -- and with few other side effects that were noted. So I spoke to my oncologist, and in June of 2016, I joined the trial.

For the next 18 months, I took 4 tazemetostat pills in the morning and 4 at night; no needles or ports required. As far as side effects, I was a little fatigued; that's it, a little more tired than I think I would have been. There was no hair loss, no burning and peeling skin, no transfusions, no infections, no neutropenia, no hospitalization, and just a little bit tired.

For 18 months, my tumors didn't grow and no new tumors developed. Best of all, I wasn't immunodeficient or toxic, and I could enjoy my family without worry, even if my grandchildren had the sniffles. Sadly though, in February of 2018, ES proved itself to be the toughest of me once again, and I had a couple of new tumors show up in my CT scan. So for me, tazemetostat was not the cure, but for 18 months, I had a fairly normal

life.

In a world where the average life expectancy of someone with metastasized epithelioid sarcoma is not very long, 18 months for a normal life is a miracle. Tazemetostat should be made available to all sarcoma warriors as a much easier, safer, and less toxic cancer treatment. With all the really bad and debilitating side effects of traditional chemotherapy used to treat ES, I believe tazemetostat should be approved by the FDA as soon as possible to get it to patients before their time runs out. Thank you for your time and letting me talk today.

DR. HOFFMAN: Thank you.

Will speaker number 2 please step up to the podium and introduce yourself? State your name and any organization you're representing for the record.

MS. NELSON: Good morning. My name is Anita Nelson. Although the company Epizyme has paid for Jeff's and my travel expenses to be here today, they are not paying for our time. I'm speaking on

their behalf. I am speaking for my husband and for all those sarcoma warriors who could benefit from this drug. Even though treatments like chemotherapy, radiation, and immunotherapy are available, they are harsh with many side effects.

Sarcoma cancer is -- [inaudible - mic fades] -- to treat, and so much more needs to be done in research, drug availability, and care. Tazemetostat and other trial drugs need to be available faster. This cancer is mean, it's cruel, it mutates, it's resistant, and it kills.

In 2011, my husband Jeff was diagnosed with soft tissue epithelioid sarcoma, proximal variant. It started in his left buttock and spread to lymph nodes and other areas in the pelvic region, many on the right side with new areas of concern on the left side. It has been a journey.

I have seen him go through so much, much of it due to the treatments we've tried to fight this disease: lack of appetite; neutropenia; nausea; C. diff; lymphedema; transfusions; a blood clot in his right leg that required an emergency flight and

an IVC filter placed; bowel obstruction; numbness; neuropathy; ruptured lymph node; bladder issues; and back pain; also IV antibiotics for more than 6 months due to a drain tube in his right side.

The disease is tough enough on its own, but adding chemotherapy, immunotherapy, radiation, and multiple surgery, it's even tougher. I have watched my husband go from a virile pipe fitter working in construction to a man that can hardly walk a quarter of a mile. He is only 52. This is supposed to be the best time of our lives. We have grandchildren to play with, but that also can be difficult and quite painful.

My husband was on tazemetostat in 2016 for only 18 months as part of a trial. He did tablets several times a day with very little to minor side effects. This allowed him to focus on his health, nutrition, lymphedema care, and regain valuable functionability. Tazemetostat kept his tumors from growing rapidly, his appetite improved, his fatigue was less, and it was the closest to normal he had been since starting treatment for this horrible

disease.

I felt it so very important to have this drug available to others who are waiting. I know of several. Time is something sarcoma patients don't have. It would give these sarcoma patients a break from harsh treatments and an opportunity to heal. This isn't a cure, but its benefits are so important on their own, especially when comparing it to other available treatments. This gives us hope and an opportunity for the physicians to get ahead of this awful beast. Thank you for your time today.

DR. HOFFMAN: Thank you.

Will speaker number 3 step up to the podium and introduce yourself? State your name and any organization you're representing for the record.

MS. GRIEGO: Good morning, members of the FDA. My name is Sandra Griego, and I take the drug tazemetostat for the treatment of epithelioid sarcoma. I testify before you today having no financial stake. Epizyme is reimbursing me for my travel so I can be here today but is not

compensating me for my time. I should tell you that this beautiful woman right here is my sister Vickie [ph], and she flew here on her own to support me while I testify.

It started in the spring of 2015. I began to experience pain in my left shoulder. Several doctors, multiple tests, anguish, frustration, worry, and not to mention increasing pain became part of my everyday life. The sarcoma is located in my brachial plexus on the left side of my shoulder, and at one point my left arm atrophied to the extent I had to use my right arm to hold my left arm. My wrists would dangle, and I couldn't even lift my elbow 5 inches from my side, and the pain was excruciating. The muscle mass in my entire left arm was nonexistent.

I should mention that I am a licensed daycare provider, and the disease made it more difficult day by day to do my job to care for the children. You don't realize the daily activities that become either difficult or even impossible for me with one hand, like tying my shoe, draining

spaghetti, and drying my hair; and for the last year, my husband would curl and comb my hair and clasp my bra. I had to learn to write with my right hand since I am left-handed, and I could no longer drive. I had to sleep on a recliner because I couldn't sleep flat because of the pain. The pain was so severe, there were times that my prayer was just to be able to sleep.

This decline continued. It was about 14 months before I was properly diagnosed with cancer, a stage 3 epithelioid sarcoma. Now that I had a diagnosis, I had to make a decision. My options were either a radical 4-quarter amputation of my left arm or to take a chance to try an experimental drug called tazemetostat.

Not liking the sound of having my arm amputated, we took the chance. Three and a half years later, although I still have sarcoma, my function and my range of motion have vastly improved. I still have pain and have to deal with nausea that comes with taking the tazemetostat, but I still have my arm. I still have my arm.

Please hear this. Like every other person who has ever heard the word "cancer," I have to ask myself why me. I now know the answer. The reason cancer chose me was because my purpose was to come before you today. As with many things, it wasn't easy. My sister flew here to support me. My husband took time off his second job so he could cover for me at my daycare job, so I could be here with you today, so I could share my story.

Tazemetostat can be another tool for doctors to give hope to their patients. Please approve this drug so that the doctors can tell their patients it's cancer, but we have a new thing that has just been approved by the FDA for you. I implore you to please approve tazemetostat, and I sincerely thank you.

DR. HOFFMAN: Thank you.

Will speaker number 4 please step up to the podium and introduce yourself? State your name and any organization you're representing for the record.

MR. KERR: Members of the FDA's Oncological

Drugs Advisory Committee, Epizyme has provided support for my travel, lodging, and reasonable out-of-pocket expenses in connection with me speaking here today. Any opinions, facts, or statements expressed are based solely on my own independent research and experiences, and are presented as my own.

Thank you all for taking the time to hear my input on this matter. My name is Joshua Kerr from Summerville, South Carolina. I'm a 15-year active and reserve veteran, I'm an engineer, I'm a son, and I'm an epithelioid sarcoma survivor. I've taken time away from work and home so that I may be here today to express my support for the approval of tazemetostat and the treatment of epithelioid sarcoma.

My experience with this disease began in 2011. The first indications that something was wrong were recurrent throat and respiratory infections, which took weeks to resolve. In a matter of months, my symptoms progressed rapidly to include severe shortness of breath; nausea;

abdominal pain; extreme fatigue and weakness; drenching night sweats; tremors; and difficulty sleeping. I was told I may have and was tested for HIV, multiple sclerosis, neurological disorders, lupus, among other life-altering diseases. It took 7 years to get an accurate diagnosis.

"You have cancer." I thought this was surely the most difficult news I would ever hear. It would only worsen when almost 3 weeks later while recovering from surgery, the pathology results arrived. I spent countless hours researching my disease. With every publication or study I read, my outlook readily progressed from nervousness and trepidation to hopelessness and fear.

I learned that currently surgery is the only option, and that frequently that surgery is amputation. I learned that ES has an extreme propensity for local recurrence and metastatic progression to the lungs and the brain, although that current radiation and chemotherapy treatments for ES have had minimal effect on long-term

survivability to date. Ultimately, one particular publication summed up all I had learned into one simple sentence. "The long-term outcome of epithelioid sarcoma is dismal."

After recovering from surgery, I immediately began adjuvant radiation. The radiation itself was tolerable for the 6 and a half weeks. At the end, the entire treated area became extremely painful, swollen, blistered, and oozed. This was accompanied by severe fatigue, loss of stamina, lymphedema, tendinosis, and an unrelenting burning. The side effects lasted from several weeks to months after the end of treatment, and some still persist today.

The psychological and emotional effects of this disease have been even more difficult to deal with. The most difficult moment I've ever experienced in my life occurred when I had to look my parents in the eye and tell them my diagnosis. Not only did their eldest child have cancer, but it was most likely to end his life early.

I'm tormented by the less obvious effects on

my life. Who would want to marry someone with this disease or these odds? Is my next MRI the one I'm told they have to amputate my arm? Does this mean I'll never know what it's like to be a father? If it spreads to my lungs, how much time do I have?

The potential side effects associated with tazemetostat are fatigue, nausea, vomiting, diarrhea, weight decrease, and anemia. As you can see, not only are many of the symptoms I experience caused directly by the disease, similar to those of tazemetostat, so too are the adverse effects of current adjuvant treatments similar. From my perspective, the side effects of tazemetostat are objectively minor and easier to deal with and more manageable than the symptoms and effects of the disease itself, and certainly better than the oppressive survival rates that face me.

In conclusion, tazemetostat provides a clear and direct benefit to current patients and fulfills an unmet need that is persistent for far too long. It has data to support its effectiveness on patient outcomes and provides a valuable option to doctors

and patients fighting an aggressive and deadly disease, which there are few effective treatment choices. I am asking the Oncological Drugs Advisory Committee to approve tazemetostat and provide patients suffering from ES, like myself, the one thing we need more than anything else; hope.

DR. HOFFMAN: Thank you.

Will speaker number 5 step up to the podium, introduce yourself, and please state your name and any organization you're representing for the record?

MS. FELSER: Good morning. Thank you for the opportunity to address the ODAC panel regarding the important progress that has been made for sarcoma patients who have had few treatment, alternatives. My name is Brandy Felser, and I'm the executive director of the Sarcoma Foundation of America or SFA.

The SFA's mission is to advocate for the development of new and better therapies with which to treat sarcoma, and we interact with government,

for-profit, and nonprofit entities to accomplish these goals. Regarding transparency, the SFA has received modest contributions from Epizyme, amounting to less than 1 percent of the SFA's annual operating budget. The vast majority of SFA fundraising is through 5K run-walks, other fundraisers hosted by patients and their families, and individual donations. Thus, the SFA has no financial interest in the success of the sponsor's application. We do, however, have an interest in supporting and advocating for promising new treatments for sarcoma patients.

As a leading sarcoma patient advocacy organization, SFA was one of few organizations that provided the patient perspective as part of Epizyme's ES collaborative patient advocate roundtable. For the past 20 years, while we have witnessed the dawning of the age of immunotherapy and molecularly targeted therapy for cancer, people with epithelioid sarcoma have been left behind, waiting for a promising new therapy that might keep the cancer in check and prolong their survival.

The drug being presented this afternoon, tazemetostat, a potent agent aimed at molecular target, common in epithelioid sarcoma, may be just that. Not only is epithelioid sarcoma one of the rarest cancers in the world diagnosed in less than 1 percent of sarcomas per year, it is one of the most aggressive. It is also a young person's disease, the median age of the patients in the tazemetostat study being only 37 years old.

Currently, there is no FDA-approved product for epithelioid sarcoma. Most patients are treated with highly toxic chemotherapy that provides very limited benefit, leaving patients with limited options, diminished quality of life, and often less than a year to live. Epithelioid sarcoma patients need more and effective treatment options.

In our nearly 20 years of existence, the SFA has interacted with many epithelioid sarcoma patients who have been in a situation faced by those who enrolled in the tazemetostat trial. Patients who have advanced disease face inevitable progression and death. Therefore, the improved

outcomes such as objective responses with durations of approximately one year represent for our patients hope for prolonged survivability. Importantly, the fact that the toxicity of tazemetostat is modest also means a better quality of life while being treated compared to that from current chemotherapy choices.

In summary, we are thankful to have a new and promising treatment option for epithelioid sarcoma patients. The addition of tazemetostat to the limited options available would provide a welcomed beacon of light to our community. On behalf of epithelioid sarcoma patients in the United States currently battling this disease, we ask you to vote to approve tazemetostat for the treatment of epithelioid sarcoma. Thank you.

DR. HOFFMAN: Thank you.

Will speaker number 6 step up to the podium and introduce yourself? State your name and any organization you're representing for the record.

DR. TRENT: Good morning. My name's Jon Trent, and I am a sarcoma medical oncologist and

associate director of clinical research at Sylvester Comprehensive Cancer Center. My travel here was supported by Epizyme, but I'm not here representing Epizyme. I canceled my clinic today so that I could be here to advocate for my patients.

Over my 17 years of practice, I've taken care of scores of patients with epithelioid sarcoma, and it often begins as a small mass on the finger, or a toe, and it works its way, marching up the extremity. It's often misdiagnosed as a benign entity, often for years, such as a wart. Once recognized as a malignant tumor, it's often surgically removed, often requiring amputations.

One incredibly frustrating aspect of epithelioid sarcoma is the exceptionally high recurrence rates; some mark at 85 percent for a primary localized tumor. These recurrences relentlessly march up the extremity and require subsequent surgical removals. This tumor is relentless; let me be clear about that. These recurrences continue and persist.

The typical patient will have 4 to 5 surgeries until an entire arm or leg is amputated. We use the terms "relentless and marching" to describe this tumor. The next recurrence after amputation is often in the pelvis or on the chest wall, and at this point, surgery and radiation are often not options, and we turn historically to standard therapies such as chemotherapy or targeted therapy such as pazopanib.

You have to realize that this tumor is also physically and psychologically tragic to patients for a primary tumor because of the aggressive surgical approaches. Fifty percent of patients will present with distant or regional metastases at the time of presentation. Patients with ES are treated with systemic therapy; we've talked about those options today: doxorubicin, pazopanib, gemcitabine, docetaxel. These agents do not have very high response rates, as we've seen in the 10 percent range.

The chemotherapy regimens are associated with high toxicity. Let me be clear that

doxorubicin plus ifosfamide, doxorubicin can result in neutropenic fever and patient death from those complications. The other therapy, pazopanib that we've discussed today, has a black box warning for liver failure, so these are toxic therapies.

In review of the tazemetostat data and from my experience, it's my opinion that this agent is as effective, if not more, than the chemotherapy and targeted therapies we've discussed today and substantially better tolerated. Moreover, the clinical benefit from chemotherapy or pazopanib is very short-lived from my experience.

These novel agents such as tazemetostat, first in category with the unique mechanism action, is desperately needed for patients with this disease. I feel so strongly about this agent that we are opening an expanded access protocol and the phase 3 protocol at our site so that we ensure patients in the southeast and south Florida have access to this medication until it is FDA approved.

Let's be honest. We know very little about this cancer; 120 new patients diagnosed each year.

We know very little. So with the strongest of terms, I support approving tazemetostat for our patients with ES. Please feel free to contact me with any questions, and I thank you for your time.

DR. HOFFMAN: Thank you.

Will speaker number 7 please step up to the podium? Introduce yourself and state your name and any organization you're representing for the record.

MS. REINKE: Good morning. I'm Denise Reinke, and I'd like to express my appreciation for having this opportunity to speak at this very important meeting. I speak today representing three different but complementary perspectives. One is as the president and CEO of SARC, the Sarcoma Alliance for Research through Collaboration, that is a nonprofit academic research consortium that facilitates the conduct of clinical trials that are investigator initiated across multicenters.

Secondly, I represent as a founding member of the Sarcoma Coalition, a relatively new

organization of sarcoma advocacy groups who have come together to strengthen the collective voice of the sarcoma advocacy community. And third, as a sarcoma nurse practitioner, I have a part-time appointment as a nurse practitioner in the sarcoma program at the University of Michigan.

My disclosures include receipt of a $10,000 unrestricted educational grant from Epizyme to SARC to support a research advocacy training program that was held by SARC. SARC has paid for my travel expenses to this meeting today, and neither the Sarcoma Coalition nor have I personally received any funding from Epizyme.

My primary purpose today is to underscore the importance of clinical research that includes rare cancers such as sarcoma, and specifically epithelioid sarcoma. We recognize that clinical trial research is the important path for assessing the potential for approving new treatments. While rare diseases collectively affect more than 23 million Americans, as we start to focus in on the subsets of rare diseases, the numbers can be very

small, making a timely and statistically meaning trial challenging. However, for patients and families dealing with uncommon diseases, who desperately need better options, access is critical.

This important work could not be done without the full engagement or the sarcoma clinical investigator community, patients, their families, as well as pharmaceutical companies willing to focus their interest and funding on rare sarcomas, such as epithelioid sarcoma. SARC and Academic Research Consortium has been engaged in collaborative sarcoma research for over 16 years, and we've learned that it's very important to have subtype specific trials to make progress.

Given the unique difference of various sarcomas, lumping subtypes together could potentially lead to missing identification of a beneficial new therapy. Hence, despite the relatively small number of patients for the sarcoma subtype like epithelioid sarcoma, trials like the tazemetostat study are important.

While improving longevity of patients with cancer as a prime importance, it is important to also identify treatments that will improve quality of life by reducing distressing symptoms associated with disease. Given that epithelioid sarcomas occur most often in young adults, effective treatment and improved quality of life can significantly impact their productive life-years at an important stage of life, not only to the individual but to our society as well. So as a representative voice of the Sarcoma Coalition, we want to clearly communicate the importance of quality, as well as quantity, of life when dealing with cancer at any age, but especially as a young adult.

Lastly, from my perspective as a nurse practitioner with 18 years of experience, caring for sarcoma patients and having hopeful therapies to help patients is important. Often patients and families, as they search for treatment options, will comment on the relative paucity of alternatives in comparison to more common cancer

types. They note there's less information, fewer trials, and rarely a trial focused only on their specific subtype.

Where rare diseases pose hurdles and challenges for clinical trial research, patients facing life-threatening cancers urgently need better options, and they are counting on us to help identify and provide them. So on behalf of my SARC research colleagues, the Sarcoma Coalition, and the many patients and families living with and dealing with sarcoma, I appreciate this opportunity to share these thoughts today for your consideration as you review and deliberate the data to consider approval of a new treatment for patients with epithelioid sarcoma. Thank you.

DR. HOFFMAN: Thank you.

Will speaker number 8 step up to the podium and introduce yourself? State your name and any organization you're representing for the record.

MS. COLLINS: Good morning. My name is Siobhan Collins, and I am a sarcoma research coordinator from the University of Colorado in

Denver, Colorado. Epizyme has covered my travel here from Colorado so that I may be here today, but please make no mistake; I am here not on behalf of Epizyme but on behalf of my patients and to provide you with my perspective as a researcher.

Sarcomas, as you know, are an extremely rare form of cancer, representing roughly 1 percent of all cancers total. Epithelioid sarcomas are an even rarer subtype of this aggressive, rare type of cancer, and as such, treatments available for epithelioid sarcomas are limited and often show little benefit.

Surgery is often one of the few options available for epithelioid patients, and I have seen several patients in our clinic alone undergo multiple surgeries over the course of only a few years, just to see their cancer return. Let me share their stories.

In June of 2016, I met Sandra in our sarcoma clinic, and she had recently been diagnosed with epithelioid sarcoma of her left arm, which was causing her significant pain, weakness, and

dysfunction. At that time, the best option for her would have been a radical left arm amputation, however, her treating oncologist that I work with, Dr. Victor Villalobos, decided first to try a clinical trial that we had available with an oral drug named tazemetostat in the hopes of at least delaying this debilitating surgery.

Sandra has now been on tazemetostat since July of 2016, with not only a large decrease in the size of her tumors, but more notably a dramatic improvement in cancer-related symptoms as well. Her ability to function with more strength and range of motion in her left arm is evident in her ability to go back to work as a daycare provider, write her name legibly, and exercise, none of which she was able to do before starting tazemetostat.

As her study coordinator for over 3 and a half years, I have witnessed firsthand her improvements and how well she has tolerated the drug. Symptoms related to the drug, mainly nausea, have been mild and very manageable with medication. The Sandra that is here with me today is not the

Sandra that I met 3 and a half years ago.

My experience working with trial patients on tazemetostat, however, has not been limited to one patient. We enrolled another patient at our site in 2017 with advanced epithelioid sarcoma who had almost an identical experience on trial that Sandra did, with the largest difference being that she had already undergone multiple surgeries just over the course of a few years.

Like Sandra, her lack of any significant side effects, coupled with the benefits that included decreased tumor size and sustained improvement in energy level, and overall better quality of life, were most notable for this patient. Unfortunately, the travel involved in her staying in the trial became too much for her and her family, and she had to come off the trial; and, unfortunately, her cancer progressed several months later.

Individual patient outcomes have varied, but all 5 patients that I enrolled at our site tolerated the treatment extremely well compared to

other trial treatments and chemotherapies we have used for sarcomas, and the majority had stabilization of their rapidly growing tumors. I can't stress enough that stable is a huge win for epithelioid sarcomas and for sarcomas in general.

In summary, treatment options for epithelioid sarcomas are severely lacking. Most often, they do not yield sustained responses and can involve multiple radical surgeries, including amputations. I have worked with investigational drugs for almost a decade over several different types of cancers. Tazemetostat stands out in my experience as an extremely well-tolerated, yet effective treatment option for patients that do not have many options at all. A more common type of cancer, such as breast cancer, has the benefit of multiple effective treatments, funding, and research. Epithelioid sarcomas do not because they are so extremely rare.

Based on the anecdotal evidence that I have provided to you, I recommend that the committee approve tazemetostat as soon as possible so that

other cancer patients are given a chance to benefit from this therapy. I would like to thank the FDA and the committee for their time and attention to this very important issue.

DR. HOFFMAN: Thank you.

Will speaker number 9 step up to the podium and introduce yourself? State your name and any organization you're representing for the record.

DR. FOX-RAWLINGS: Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I am Dr. Stephanie Fox-Rawlings, the center's research manager. Our center analyzes scientific and medical data to provide objective health information to patients, health professionals, and policy makers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

We can all agree that there is a need for better treatment options for patients with epithelioid sarcoma. We can also agree that new treatments still need to have a real and meaningful

benefit to patients. Just as important, there needs to be enough information about the treatment so that patients and their physicians can determine if the benefits outweigh the risks for each patient, so they can decide whether or not to try it.

There can be differences of opinion on what would be a meaningful benefit and what would be a likely risk, and those will vary for individual patients. Unfortunately, there is limited information about the benefits of this drug. There is only one clinical trial with two cohorts that have different eligibility criteria and different primary endpoints. Only 11 to 15 percent of the patients in those cohorts had a decreased size of lesions with variation in the time to response and duration of response.

Based on the data discussed today, it is difficult to determine how well the treatment works and whether the effect is clinically meaningful. A major problem is the lack of a good control group. In this study, there was no internal comparison

group, and the options for historical controls that were provided differed from the current study in terms of patient selection, study design, measurement of response rate, and/or when the study occurred. In other words, the control groups were different enough that they are not very informative.

Another major problem is that the study doesn't provide direct information about patient survival or quality of life. A decrease in tumor size is desirable, but it may not be meaningful for patients if it isn't associated with a better quality of life or long-term prognosis. So the level of benefit that patients receive from a decrease in just tumor size is unclear.

Unfortunately, there are a lot of adverse events associated with drug. Some of these adverse events were serious, including the potential for secondary cancers, but many of the less serious adverse events are also likely to reduce patient's quality of life. These risks may be acceptable for some patients if the treatment provided a

meaningful benefit. The purpose of the day's meeting is to weigh those likely risks compared to the benefit of tumor shrinkage for 11 to 15 percent of patients.

Some might say that since the current treatment options are poor, any new treatment should be approved, even if it only provides hope. But if the mission of the FDA was merely to provide hope, they would approve placebos, as well as every new drug. The FDA needs to maintain high standards for approval. This advisory committee is asked to advise the FDA if there's sufficient scientific evidence that the benefits outweigh the risks for most patients; or if not, if there's a proven subgroup of patients that the drug could be approved for.

If you can't conclude that the benefits outweigh the risks for a defined group of patients, please consider advising the FDA on the kind of evidence needed to provide that evidence prior to approval. It can be much harder to obtain this data after a drug is approved. Thank you for your

time.

Clarifying Questions to Presenters (continued)

DR. HOFFMAN: Thank you. The open public hearing portion of this meeting is now concluded and we will no longer take comments from the audience. I do want to allow a couple of minutes to have some clarification. I was asked to allow that, and also to mention that Dr. Tap is not going to be participating by phone as we originally thought. Dr. Ward I think wanted to clarify something, and then Dr. Agarwal had some answers to some questions that she hadn't previously had.

DR. WARD: Thank you. Ashley Ward, FDA. I wanted to clarify the FDA's consideration of stable disease and point out that the FDA agrees with both the patients and the providers that have been discussing stable disease today, that prolonged periods of stable disease can absolutely represent an important and meaningful outcome for patients with epithelioid sarcoma.

The issue that the FDA was trying to communicate was that we don't feel that stable

disease can be measured on a single-arm study. Stable disease is usually assessed as part of the endpoint progression-free survival, which necessitates randomization to be able to account for patient level differences in disease course.

DR. HOFFMAN: Thank you. I think some questions have been put to Dr. Agarwal that she didn't have the answers to earlier, and she wanted to provide them.

DR. AGARWAL: There was a question about the therapies that were used after discontinuation of tazemetostat. Here's the breakdown of all the therapies that were used, and as you can see, most of these patients are under what drugs that are commonly approved or used. I believe a lot of these therapies are the ones that we just talked about. I think it's important to understand that because there are these generic therapies, many of the patients actually continued post progression on tazemetostat.

I would like to invite Dr. Demetri to provide some insight on this aspect of

post-progression of use of tazemetostat and the fact that there are just these basic therapies that are used.

DR. DEMETRI: George Demetri, Dana-Farber. I would like to just simply add what we've already talked about, that patients and physicians together decided to continue this agent despite a RECIST-defined progression. At some point, the investigators, well beyond me, many investigators across the world who participated in this, decided to move on to other therapies.

DR. AGARWAL: I think the second question about any specific data on disease progression before treatment, as we talked about earlier, it's very hard to collect this data. What we have is our last treatment and the duration of the last treatment, which was 2.4 median, which I've already indicated to you. But we don't have data in terms of the trajectory of that treatment before tazemetostat.

DR. HOFFMAN: Dr. Uldrick, did you have a question?

(Dr. Uldrick gestures no.)

DR. HOFFMAN: Okay. I had a question for Dr. Demetri. The FDA's review had mentioned some liver toxicity dose interruptions for abnormal transaminases, and I hadn't heard about that earlier. Were these significant or relatively minor?

DR. DEMETRI: George Demetri, Dana-Farber. These were relatively minor. These led to temporary interruptions of dosing. Sorry about that; there are a few of these up here. I don't think we need the slides. Any AE leading to dose reduction was only one.

This is not the right slide; forget the slides. Honestly, I've reviewed the data. There are temporary several day interruptions when the protocol-defined liver tests would go up, and then they come down a few days later. This was nothing that led to any sort of Hy's law or anything else.

Now that we have a slide here, let me just point -- there we go. In the primary population of all grades, there were a few that were at grade 3;

3 percent of 62 is a very small number that came and went. We did not do anything other than a temporary, several day discontinuation of the drug that then restarted as per the protocol rules.

DR. AGARWAL: Can I just add a little bit? In terms of this AST/ALT, there were 3 patients who led to interruptions, and all these patients had liver mets. They're either bowel obstruction or liver mets interruption for less than 2 weeks, and it is logged.

DR. HOFFMAN: Dr. Sung, did you have another question?

DR. SUNG: As I understand, Cohort 6 was designed to explore the immune priming effects of the study drug. Is there any data from that available?

DR. AGARWAL: Cohort 6 was added after Cohort 5 was started. We required mandatory biopsies. The trial is ongoing. We are still collecting data. As I mentioned earlier, we have still patients ongoing, so we are in the process of collecting that data.

DR. SUNG: But you should have the biopsies, right? Because you did a biopsy beforehand and you did a biopsy right after treatment starts. So all these patients have been followed on study for several months.

DR. AGARWAL: The cohort actually completed in May of this year. Although the study started, it finished May this year, so we have biopsies. We have [indiscernible] data. It's ongoing.

DR. HOFFMAN: Dr. Halabi?

DR. HALABI: Thank you. I had a question for the FDA. I would appreciate clarification on the accelerated approval program. It's my understanding that this program is for drugs that have been developed for diseases with unmet need, and usually those are based on a surrogate endpoint. So the key question here is, is there a deadline or a timeline on when the sponsor should complete the phase 3 trial?

DR. PAZDUR: No, nothing is stated specifically as far as time. The only caveat is that these studies should be done with due

diligence.

DR. HALABI: Thank you.

DR. HOFFMAN: Are there any other clarifying questions before we move to our discussion of the questions?

(No response.)

Questions to the Committee and Discussion

DR. HOFFMAN: Okay. We'll now proceed with questions to the committee and panel discussions, and I would like to remind the public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

The question -- it's on the screen -- is for us to please discuss whether the evidence from Cohorts 5 and 6 of EZH-202 is sufficient to establish the benefit of tazemetostat in patients with epithelioid sarcoma. If there are no questions or comments considering the wording of the question, we'll open it to discussion.

Dr. Hinrichs?

DR. HINRICHS: To me, a major part of this

question comes down to the clinical activity of the drug. To get a discussion about that started, I'd like to ask the members of this committee, who are specialists in this disease, to comment on the response rate and the stable disease that was observed and, basically, what you think of the tumor curves.

DR. MEYER: Christian Meyer from Johns Hopkins, a medical oncologist who cares for sarcoma patients. I certainly would echo a lot of the commentary from other oncologists that the disease is relentless and progressive. I certainly haven't seen the type of responses presented here with this data, not in terms of the stable disease and all the complications that come with that interpretation, but just in terms of people actually having responses on the drug. I have not seen this disease spontaneously regress, so the drug is having some effect.

Certainly, when I have a patient in the room counseling them on treatment going forward, going back to an earlier comment about equipoise, what

I'm able to say to them is I honestly have no data for you for epithelioid sarcoma, so we're kind of wide open in terms of what I would consider treating you for. So it's a balance of kind of help and harm.

Certainly, the standard therapies that have been mentioned here several times today come with significant side effects. I'm not discounting any of the grade 3 or grade 4 that were presented here, but relatively speaking, they're minor compared to the side effects that were presented with tazemetostat. So in my mind, simply the stable disease and the partial responses are something I've not seen in the other therapies that are currently available for me to give.

DR. HOFFMAN: Dr. Riedel?

DR. RIEDEL: Rich Riedel from Duke University. Just to make a couple of quick comments, the things that struck me, to address your question directly, to me a response rate as shown in this trial of 11 to 15 percent, depending on the cohort that you looked at, is considered

clinically meaningful, in my opinion: pazopanib, a response rate of 4 percent across a broad range of unselected sarcomas; doxorubicin, depending on the study that you look at, a response rate of 5 percent to perhaps 20 percent across a broad range of unselected sarcomas; and I can almost assure you, although I don't know this with certainty, that epithelioid sarcoma was not heavily represented in either of those studies.

So in the end, you're left with the clinical experience of experts in the room who universally have conveyed the message that this is a relentless disease that does not respond to standard of therapy. As I look at the first and only prospective clinical trial in epithelioid sarcomas showing a response rate of 11 to 15 percent, what I'm struck by is not only the response but also the durability of those responses. Patients who are enrolled in this study, 95 percent were progressing -- however you want to define that -- prior to study entry. In the meantime on their prior therapy, which is a standard therapy,

it was 2 and a half months, wholly inadequate.

Lastly, I'll just say that my mantra -- and I think this was mentioned earlier -- is that stable disease is important. My mantra in clinic -- and I tell every patient this -- is that stable disease is a good thing, and I try to set up an expectation early that stable disease is something that we're more likely to see rather than a response. This is for all sarcomas. If I get stable disease with epithelioid, I'm ecstatic because we don't see it often.

DR. HOFFMAN: Ms. Webb, do you have a comment?

MS. WEBB: I guess I just wanted to, first of all, echo what Dr. Riedel and Dr. Meyer were saying regarding the overall response rate and the durability of it as well. I think that's on slide 72. With being able to keep it at 76 months with 64 percent, that's a dream for a lot of us. Those are probably the first two if I could boil down the elements, from what I read, the issues, the response rate, durability.

Also, one of the concerns I think the FDA has is with the secondary malignancies, but from what I understand, doxorubicin also has secondary malignancies. With all of the information that you provided, those were all patients that also took multiple therapies as well.

So I guess what I'm getting at is when we're given a choice by our oncologist, we understand that there are a lot of risks with these medicines. They're hard medicines to be taking, and there are risks that we're going to have to address. But we would like the opportunity to be able to discuss that with our oncologist and be able to look at those risks and understand them, but at least be given a choice. I think that the other elements are proving that this would be an effective benefit.

The other part of this I think is also looking at the safety or toxicity of this drug. I think it's pretty clear that this drug has so much less -- it brings us so much more quality of life, so we're actually able to go out and do things, and

we're not impacted as much with some of these horrific secondary issues that the drugs cause.

There's one other element that hasn't been discussed today. For example, I have another a friend that has epithelioid sarcoma that has reached his maximum dose of doxorubicin, and he's just now finished with pazopanib. It's no longer working. So what choices does he have? There really isn't much. There's really nothing available, right? So they're working through that, but tazemetostat would give us another option. I think that's important to add that to our arsenal. Thank you.

DR. HOFFMAN: Yes?

DR. LEMERY: Steve Lemery, to clarify why we bring up the secondary malignancies. I mean, this is a public discussion, just to point out that this has happened. We fully understand in this disease, especially with the relatively short life expectancy in patients with this disease, this is less of an issue for this disease. But we do think it's important to be completely open about all the

effects that have been observed with use of this drug.

I think from the agency's standpoint, the biggest issue is the uncertainty given the single-arm trial and really being able to communicate to a patient what the toxicities are or whether there are potential rare toxicities that we're not aware of. But I think the secondary malignancies is not the be end all for us, especially for this patient population.

DR. HOFFMAN: Dr. Uldrick?

DR. ULDRICK: The thing I'm struggling most with is trying to understand how to think about the stable disease, and I was hoping that, again, our colleagues who treat more sarcoma could help me understand this. In terms of this specific rare sarcoma, it seems that there may be a variability in the natural history. We've heard some stories where it takes many years to even be diagnosed with the disease.

I'm just curious as to your thoughts as to whether the patient population selected for this

study potentially included people whose natural history would have been longer. I think that the median number of lesions were relatively small. The target lesions were about 5 and a half centimeters on average. Is it possible that the stable disease observed in a patient population with that tumor burden is consistent with the natural history of epithelioid sarcoma?

DR. RIEDEL: Rich Riedel from Duke. In my experience, the more indolent course of the disease occurs in individuals with localized disease as opposed to those with metastatic disease, which is the patient population that we're talking about. So in my experience, it's not unusual for someone who has a localized lesion, multiple surgeries, but when they develop metastatic disease, there can be a change and the pace of the disease can increase.

I don't know if I could specifically answer your question for what you're asking except to say that, in my experience, it's not the case for metastatic disease. I don't see a waxing and waning, a stabilization; it's just a progressive

march.

DR. HOFFMAN: Dr. Halabi?

DR. HALABI: What I'm struggling here with is the clinical benefit because the study, you had only 9 patients in Cohort 5 who responded. And even though the median duration of response was 16.4 months, the median progression-free survival was less than 4 months. So I'm trying to understand the data, and the key question here is whether stable disease could be a measured or a proxy measure of clinical benefit.

I'm following up to Dr. Uldrick's comment. So can the clinician try to help me understand the data? Because you have only 9 patients who responded out of 62, and even though the median duration is 16 months, duration of response, the median PFS was, I believe, 16 weeks.

DR. HOFFMAN: Dr. Meyer?

DR. MEYER: Thank you. Christian Meyer from Johns Hopkins. I'll try to comment on both of those questions. Getting back to the natural history of the disease that you asked before, it is

true, there can be a slower pace, slower burden of disease. And I'd agree with Dr. Riedel that that's typically more in the localized setting.

The other thing I might want to point out about the target legions commentary in this particular disease is that we don't necessarily see large lesions all the time. So there can be patients that are just dotted with smaller tumors, and they're not always these gigantic tumors that people may think about with sarcomas. So that aspect of it brings questions about burden of disease, but people can have heavy burdens of disease with very small tumors in this particular entity.

Then, going back to the question about stable disease, I guess, one thing that at least impressed me in terms of the responses were that the people that responded had durable responses. I guess in Cohort 5, in those 9 patients, the median duration of response I want to say was about 69 or 70 weeks there. So you selected a population of people that have had a response to a drug and

maintain that response, knowing that anything else we have to poorly compare it to, when all these other trials that aren't set up to compare, we don't see that type of duration.

So in my clinical experience, having somebody take let's say doxorubicin for 6 cycles, in most studies with doxorubicin, the average progression-free survival is somewhere between 4 and 6 months. So that essentially means is that you've taken 6 cycles of doxorubicin, for 4 and a half months, you're done, and you progress, and you've got to go on to something else. That's what that means in the real-world clinic, which is unfortunate but true.

So what's striking is that some of these people that actually had their tumors shrink maintain their response, which does sway me a little bit in terms of the benefit this is giving to the people that respond.

DR. HOFFMAN: Dr. Sung?

DR. SUNG: If I understand correctly, it appears that there are two different settings.

There's the frontline setting, which as the FDA has pointed out, it becomes very hard to evaluate stable disease. It becomes very hard to evaluate what the natural history of the disease would have been, and it becomes very hard to compare results with this therapy as opposed to other established therapies.

However, in the second-line setting, where the disease is already progressing through doxorubicin or pazopanib, where the patient has already failed those things, to have stable disease in that setting I think becomes much more meaningful if you are looking at, as Dr. Hinrichs was saying, the trajectory, because in those settings, the trajectory, it's getting worse and it's stopping.

Is that correct?

DR. RIEDEL: In my experience, the trajectory is fast in the frontline setting. It's in the localized disease setting where it can be more indolent. So for me, it's frontline metastatic, second-line metastatic. It's all bad,

which is why I think there's enthusiasm, or at least my potential enthusiasm, for a drug like this; that even if stable disease, it's what happens for the majority of patients. The other thing I would point out is 70 percent of patients with some decreased size and target burden is pretty impressive for this disease, in my opinion.

DR. HOFFMAN: I'd like to comment as I guess someone who's been in oncology longer than I care to mention. With respect to the way we measure and grade responses, that it's certainly the case with some of the targeted drugs, that we'll often treat beyond progression if there's an additional lesion that is not symptomatic because sometimes patients can continue to be having benefit even if there is an additional lesion.

There are different criteria for the immunotherapy drugs that are coming into play. I certainly don't know enough about the chemistry of this drug to know about whether epigenetic phenomena take longer and how that plays into it. But I do have the sense as a clinician that stable

disease is often very meaningful to patients. Their lives may be extended even if it's not a measurable reduction. But I do think that some of the standard criteria by which we measure response, with some of the newer drugs that we're looking at in the last number of years, maybe those are not the best criteria to make decisions in all cases.

Dr. Riedel?

DR. RIEDEL: Rich Riedel from Duke. Just to follow up on that, that is true. Particularly in sarcoma, our experience with antiangiogenic agents, i.e., pazopanib, tell us that RECIST probably is not the appropriate measure of response. Some people have looked at things like Choi criteria, for example, where you can actually see a paradoxical increase in the size of the tumor with an associated hypoattenuation on imaging.

I don't know if it's appropriate to ask the sponsor or not, but I was wondering if there were any alternative radiologic assessments, i.e., were there any Choi responses seen or not? I don't know if we can ask that or not.

DR. HOFFMAN: We can ask if someone wants to address that.

DR. AGARWAL: Shefali Agarwal. Those were not performed in this study.

DR. HOFFMAN: Other questions or comments?

(No response.)

DR. HOFFMAN: We can close the discussion regarding this question. Our second question is the one that we'll be specifically voting on today, and that is, does the demonstrated benefit of tazemetostat outweigh the risks of the drug in the proposed indication that the applicant is proposing?

First, if there are no questions or comments about the wording of the question, we will now open this to discussion. Any comments about the wording of the vote question?

(No response.)

DR. HOFFMAN: Okay. We can begin discussion of that.

DR. HOTAKI: If you guys want to just discuss the question, just not say how you're going

to vote if there's anything that you want to comment about the question, or we can just move to voting if no one has any other further --

DR. HOFFMAN: You have your card -- oh, okay.

We'll be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you're unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we'll go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to.

Any comments about the process?

(No response.)

DR. HOFFMAN: Okay. Please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. HOTAKI: For the record, the vote is 11 yes, zero noes, zero abstentions.

DR. HOFFMAN: That's unusually uniform.

(Laughter.)

DR. HOFFMAN: Now that the vote is complete, we'll go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record. Should we start with Dr. Riedel?

DR. RIEDEL: I voted yes. For me, it's what I perceive to be a clinical benefit and meaningful benefit to patients. As we've mentioned, stable

disease is a good thing. There's clearly a proportion of patients who get response that's durable. It's an oral therapy that appears to be well tolerated.

DR. MEYER: Christian Meyer. I voted yes. I voted yes for many of those same reasons. It was in my opinion that it provided a meaningful benefit to patients, as well as the fact that it was the first trial that looked prospectively at this disease going forward with some data on response rates that we can use, hopefully, in a productive fashion for further trials.

MS. WEBB: I voted yes for those same reasons.

DR. HAWKINS: Randy Hawkins. Yes, well spoken. I think part of the problem is it can induce bias, in my thinking, against this type of trial because of small numbers, but it's not actually fair if you have a very, very rare disease. So I was impressed enough to say we should have this added to the toolkit of the oncologists and the recommendation by clinicians on

the panel.

DR. SUNG: Anthony Sung. I voted yes for many of the reasons my colleagues described, particularly in the second-line setting. I still remain unconvinced by the data in the first-line setting that this is superior to other existing therapies like doxorubicin or pazopanib. I do think there would be room for, say, approval in the second-line setting, which would also leave room for the proposed randomized clinical trial to occur and take place in the frontline setting, because I think that question is still undecided.

Finally, I would just make a comment to the sponsor that I would hope they build in quality-of-life studies into the RCT because I think it's come up multiple times before ODAC, where sponsors suggest that there is a better quality of life or benefit, but they do not have the data to back that up.

DR. ULDRICK: Thomas Uldrick. I voted yes as well due to the demonstration of a small tumor regression rate in a disease for which that doesn't

seem to happen with other therapies. It's the first study to show this perspectively. I guess for a disease with only 120 patients per year, I think the real way to move the bar forward is, really, continued clinical trials and clinical studies. I think that the community of patients with this disease and the doctors who treat them deserve some better evidence to figure out how to use this drug.

So I really think that it's important to see the clinical trial go forward and for further data to be gathered on the possibility that leads to stabilization of disease.

DR. CRISTOFANILLI: Cristofanilli. Of course I was yes, and maybe for similar reasons. I was convinced by the efficacy in patients with refractory disease that progressed on prior therapy. For oncology, there's always an indication of activity, so this drug has some activity. Maybe the response rate doesn't reflect that. It seems like the stability of the disease may reflect that in this disease with a short

survival.

Clearly, maybe with the rare disease, continuation of a clinical trial registry to follow these patients over time, more patients will be treated to especially understand the impact on quality of life and the safety. We don't have a better understanding now, and I'm a little bit concerned on the randomized study recommendation with doxorubicin, but time will tell.

DR. HOFFMAN: I'm Philip Hoffman. I voted yes. I believe that although the response rate is low, I was also impressed, as a few others have mentioned, about the duration of some of those responses. I'm also impressed that this does appear to be safe. While the concern for second malignancies is out there, it seems quite rare. The natural history of patients with advanced sarcoma is such that I think the consideration of secondary malignancies is really not very important to that group of patients.

DR. HALABI: Susan Halabi. I also voted yes. Obviously, there is an unmet need, and this

is a rare disease. The data did show some modest response among a total of 14 patients in both Cohorts 5 and 6. I was also concerned about risk of developing secondary malignancies, but, again, the data is missing, and definitely there needs to be a longer duration of follow-up for the patients enrolled on both Cohorts 5 and 6.

This last comment is more for the sponsor. I hope that you will pick up a clinically meaningful endpoint in your phase 3 trial because I'm not convinced that PFS is your best endpoint, and I don't have the answer to what the best endpoint is going to be.

(Laughter.)

DR. HALABI: Also, I'm not sure 130 patients is sufficient.

DR. HINRICHS: Christian Hinrichs. I voted yes. I'm left overall with the impression that the drug has striking clinical activity in a really aggressive disease that is hard to interfere with its natural course. This is despite the number for the response rate being relatively low. I think

that this reflects a limitation in the way that we measure disease responses now with RECIST being our best tool, but I think many of the experienced oncologists on the panel and in the room recognize the limitations of that tool.

I think that also there are some patients who clearly benefit, and benefit with nice and durable responses. That they benefit is further supported by considerations related to the safety of the drug. I am impressed by the low rate of discontinuation of the drug. It's really remarkable. The possibly most concerning safety issue related to secondary malignancies, I don't see as a major problem in the context of this aggressive primary malignancy.

DR. KLEPIN: Heidi Klepin. I voted yes for all of the same reasons I think were already articulated. I think the data was sufficient to show a clinically meaningful effect with durable responses and at least a subset of the patient population who have a very high morbidity and high mortality disease with few other options. So I

think that's sufficient.

I was also impressed that the safety data appeared to demonstrate tolerability, so I think this is an option for patients in this setting. I struggled a little bit with whether or not the blanket approval -- as was mentioned by Dr. Sung as well, the data I think best supports approval in the second-line setting based on the population studied.

If it's approved in the first line, all lines of therapy, this, as I'm hearing the conversation, could move into being the standard of care for a lot of patients and practice, if I understood some of my colleagues discussion, in which that does reflect on the proposed phase 3 trial and the conversation around, one, would you have difficulty enrolling in the current design, and if so, does that comparator arm need to change?

So it's just something to think about; and also echoing the comments about strongly encouraging the sponsor to include patient-reported outcome data. We talk about the benefits to the

patient, and we never show the data, and there are sufficient validated tools to do so. The FDA has really led the way in demonstrating how they can be used in clinical trial designs. So if you haven't already incorporated that, I would strongly advocate that you do.

DR. HOFFMAN: To summarize, I think, obviously, the vote is overwhelmingly positive. I think there was agreement that although this is a rare disease, it's a very difficult disease. There aren't a lot of good tools for it, and this does represent an additional tool.

I think some of the limitations that people voiced I think are real, that we don't have as much information as we might like about the quality-of-life issues, patient-reported outcomes issues, and whether progression-free survival is the best way to assess this, especially if there is also the issue about where does stable disease fit in the overall assessment of clinical benefit.

I do think certainly the positives are that this was a prospective trial. It's an unmet need

for sure. The adverse events do not appear to be, certainly, life threatening and only rarely lead to any patient discontinuation or even delays. I think we do need further clinical trials about this. Because this is such a rare disease, and if there are 120 patients per year in the United States, I don't see this as the beginning of a slippery slope of this drug being used inappropriately in this patient population. We're approving it, or we're recommending approval, based on a very limited indication, and I think further indications will probably come up over the years and deal with them at that point.

Are there some final comments from the FDA?

DR. PAZDUR: No. Thank you.

Adjournment

DR. HOFFMAN: So we will now adjourn the meeting. Panel members, please leave your name badge here on the table so it can be recycled. Please also take your personal belongings with you. The room will be cleaned at the end of the meeting day, and any materials left on the table will be

disposed of. I thank everyone for their time and participation.

(Whereupon, at 11:56 a.m., the meeting was adjourned.)