FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Tuesday, December 17, 2019

Morning Session

8:00 a.m. to 11:28 a.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Lauren Tesh Hotaki, PharmD, BCPS, BCIDP
Division of Advisory Committee and
Consultant Management
Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Massimo Cristofanilli, MD, FACP
Associate Director of Translational Research and
Precision Medicine
Robert H. Lurie Comprehensive Cancer Center
Chicago, Illinois

Susan Halabi, PhD
Professor of Biostatistics and Bioinformatics
Duke University Medical Center
Durham, North Carolina

Christian S. Hinrichs, MD

Investigator & Lasker Clinical Research Scholar

Experimental Transplantation and Immunology Branch

National Cancer Institute

National Institutes of Health (NIH)

Bethesda, Maryland

Philip Hoffman, MD

(Chairperson)

Professor of Medicine

The University of Chicago

Section of Hematology/Oncology

Department of Medicine

Chicago, Illinois

Heidi D. Klepin, MD, MS

Associate Professor of Internal Medicine

Section of Hematology and Oncology

Wake Forest University Health Sciences

Winston Salem, North Carolina

Anthony D. Sung, MD

(Morning Session Only)

Assistant Professor of Medicine

Duke University School of Medicine

Duke Adult Blood and Marrow Transplant Clinic

Durham, North Carolina

Thomas S. Uldrick, MD, MS

Deputy Head, Global Oncology

Associate Member, Vaccine and Infectious Disease Division

Associate Member, Clinical Research Division

Fred Hutchinson Cancer Research Center

Seattle, Washington

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBER

(Non-Voting)

Albert L. Kraus, PhD

(Industry Representative (alternate))

Global Regulatory Portfolio Lead, Oncology

Pfizer, Inc.

Guilford, Connecticut

TEMPORARY MEMBERS (Voting)

Dawn Aldrich, PhD

(Patient Representative; Morning Session Only)

New Rochelle, New York

Randy W. Hawkins, MD

(Acting Consumer Representative)

Department of Internal Medicine

Internal Medicine/Pulmonary & Critical Care

Charles R. Drew University of Medicine and Science

Los Angeles, California

Matthew H. Kulke, MD

(Morning Session Only)

Zoltan Kohn Professor

Department of Medicine

Boston University School of Medicine

Co-Director, Boston University-Boston Medical

Center Cancer Center

Boston, Massachusetts

Diane Reidy Lagunes, MD

(Morning Session Only)

Medical Oncologist

Division of Gastrointestinal Oncology

Memorial Sloan Kettering Cancer Center

New York, New York

Hanna K. Sanoff, MD, MPH

(Morning Session Only)

Associate Professor

Department of Medicine, Division of

Hematology/Oncology

University of North Carolina (UNC)

Clinic Medical Director, UNC North Carolina

Cancer Hospital

Chapel Hill, North Carolina

FDA PARTICIPANTS (Non-Voting)

Richard Pazdur, MD

Director, Oncology Center of Excellence (OCE), FDA

Acting Director, Office of Oncologic Disease (OOD)

Office of New Drugs (OND), CDER, FDA

Steven Lemery, MD

(Morning Session Only)

Acting Director

Division of Oncology 3 (DO3)

OOD, OND, CDER, FDA

'Lola Fashoyin-Aje, MD MPH

(Morning Session Only)

Acting Deputy Director

DO3, OOD, OND, CDER, FDA

Martha Donoghue, MD

(Morning Session Only)

Cross-Discipline Team Leader

Gastrointestinal Cancers Team

DO3, OOD, OND, CDER, FDA

Naomi Horiba, MD, MPH

(Morning Session Only)

Clinical Reviewer

Gastrointestinal Cancers Team

DO3, OOD, OND, CDER, FDA

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've not already done so. I would also like to identify the FDA press contact, Brittney Manchester. If you're present, please stand. Thank you.

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

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

DR. LEMERY: Steven Lemery, acting director, Division of Oncology 3.

DR. FASHOYIN-AJE: Lola Fashoyin-Aje, acting deputy director, Division of Oncology 3.

DR. DONOGHUE: Martha Donoghue, clinical team lead, Division of Oncology 3.

DR. HORIBA: Naomi Horiba, clinical reviewer, Division of Oncology 3.

DR. SANOFF: Hanna Sanoff, GI medical oncologist at University of North Carolina.

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

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

DR. HOTAKI: Lauren Hotaki, designated federal officer.

DR. HOFFMAN: Philip Hoffman. I'm a medical oncologist at University of Chicago.

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

DR. ULDRICK: Thomas Uldrick, medical oncology, Fred Hutchinson Cancer Research Center.

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

DR. ALDRICH: Dawn Aldridge, Solutions Cancer Resource Center in New York.

DR. REIDY: Diane Reidy, medical oncologist from Memorial Sloan Kettering.

DR. KULKE: Matt Kulke, hematology-oncology, Boston University.

DR. KRAUS: Albert Kraus, industry representative for today, Pfizer.

DR. HOFFMAN: 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 if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic

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

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

DR. HOTAKI: Just quickly for the record, Dr. Hinrichs, do you want to introduce yourself?

DR. HOFFMAN: Oh, sorry.

DR. HINRICHS: Christian Hinrichs. I work at the National Cancer Institute.

Conflict of Interest Statement

DR. HOTAKI: The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting

members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs 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 service 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; patent and royalties; and primary employment.

During the morning session, the committee will discuss supplemental new drug application 208558/010 for Lynparza, olaparib, tablets submitted by AstraZeneca Pharmaceuticals LP. The proposed indication, use, for this product is for the maintenance treatment of adults with deleterious or suspected deleterious gBRCAm metastatic adenocarcinoma of the pancreas, whose disease has not progressed on the first-line,

platinum-based chemotherapy.

This is a particular matters meeting during which specific matters related to AstraZeneca's supplemental 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.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Jonathan Cheng, the standing industry representative, has self-recused from participating in this session of the meeting. The alternate industry representative, Dr. Albert Kraus, is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Kraus' role at this meeting is to represent industry in general and not a particular company. Dr. Kraus is employed by Pfizer.

To ensure transparency, we encourage all

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

DR. HOFFMAN: We will proceed with the FDA's introductory comments from Dr. Martha Donoghue.

FDA Opening Remarks - Martha Donoghue

DR. DONOGHUE: Good morning. My name is Martha Donoghue. I am a pediatric oncologist and team leader for the gastrointestinal cancer's team in the Division of Oncology 3, in the Office of Oncologic Diseases. I would like to extend my thanks to the members of the advisory committee,

the AstraZeneca team, invited guests, visitors, and FDA colleagues for attending and participating in today's discussion of this supplemental application for olaparib, NDA 208558. In my introductory comments, I will provide a brief background on this application; FDA's reasons for requesting input from the committee; and the issues that FDA has identified for consideration during today's discussion.

Olaparib is a poly ADP-ribose polymerase, or PARP, inhibitor, approved for multiple indications, in the maintenance or non-maintenance settings, for the treatment of patients with deleterious or suspected deleterious germline or somatic BRCA-mutated, advanced epithelial ovarian and HER2 negative metastatic breast cancer.

AstraZeneca seeks approval of olaparib for the maintenance treatment of adult patients with deleterious or suspected deleterious BRCA-mutated metastatic adenocarcinoma of the pancreas, whose disease has not progressed following first-line platinum-based chemotherapy.

Patients with germline BRCA mutations comprise approximately 5 percent of patients diagnosed with pancreatic cancer. Although the natural history and prognosis of patients with germline BRCA-mutated pancreatic cancer have not been well characterized, published studies suggest that patients with germline BRCA-mutated metastatic pancreatic cancer have a better prognosis compared to patients without a germline BRCA mutation.

There are currently no drugs approved for treatment of pancreatic cancer in the maintenance setting irrespective of germline BRCA mutation status. Some treatment guidelines recommend maintenance systemic therapies or drug-free intervals among the options for managing patients who do not experience disease progression after at least 4 to 6 months of first-line chemotherapy.

Results of the POLO trial provide the primary evidence to support the safety and effectiveness of olaparib for the proposed indication. As depicted in this slide, POLO is a double-blind, randomized, placebo-controlled,

multicenter trial that randomized 154 patients to receive either olaparib 300 milligrams orally, twice daily, or matching placebo until disease progression or unacceptable toxicity.

The primary efficacy outcome measure for the POLO trial was progression-free survival, or PFS, according to blinded, independent central review using the response evaluation criteria for solid tumors, RECIST, version 1.1. The primary analysis of POLO demonstrated a statistically significant improvement in PFS in patients randomized to receive olaparib compared to patients randomized to placebo. The hazard ratio for PFS was 0.53 with a 95 percent confidence interval ranging from 0.35 to 0.81, corresponding to a median improvement in PFS of 3.6 months.

POLO was designed to have 80 percent power to detect a hazard ratio of 0.57 for overall survival, or OS, based on 106 events, assuming a median overall survival of 8 months in the placebo arm and 14 months in the olaparib arm. A prespecified interim analysis of overall survival

conducted at the time of the primary PFS analysis did not show a statistically significant difference between the treatment arms.

In general, the safety profile of olaparib observed in POLO was consistent with the known adverse reaction profile of olaparib. Patients randomized to olaparib experienced a higher incidence of fatigue, gastrointestinal toxicities, anemia, decreased appetite, and rash. Additionally, there was an increase in the incidence of serious adverse events.

FDA referred this application to the advisory committee primarily because it relies upon the results of a single small trial that demonstrates a modest improvement in progression-free survival with no overall survival benefit observed. Prior FDA approvals in pancreatic cancer have been supported by demonstration of an improvement in OS.

FDA has considered overall survival to be the preferred efficacy endpoint in pancreatic cancer because it is a direct measure of clinical

benefit. It is generally a feasible endpoint due to the relatively short life expectancy of patients with metastatic pancreatic cancer and because there are potential limitations in the assessment of PFS in pancreatic cancer. If approved, the supplemental application would be the first time FDA has approved a drug for the treatment of pancreatic cancer based upon demonstration of improvement in PFS.

FDA has identified two issues related to the risk-benefit assessment of olaparib in this application, which will be described in the next few slides. The first issue relates to whether the observed magnitude of improvement in PFS is a reliable estimate of the treatment effect of olaparib.

The 95 percent confidence interval for the point estimate of the hazard ratio for progression-free survival is relatively wide, ranging from 0.35 to 0.81, reflecting a degree of uncertainty regarding the magnitude of the PFS effect of olaparib. Additionally, there is

uncertainty regarding the precision with which tumor burden can be assessed by conventional imaging in pancreatic cancer.

As noted in FDA's December 2018 guidance for industry on clinical trial endpoints for the approval of cancer drugs and biologics, accuracy in measuring tumors can differ across tumor settings, and tumor measurements can be imprecise in locations where there is a lack of demarcated margin.

Assessment of tumor shrinkage and growth, particularly at the primary site of the pancreas and some metastatic sites such as the peritoneum, may be difficult in some patients. This confers a degree of uncertainty regarding the observed PFS results.

Uncertainty regarding the accuracy of radiologic assessment of PFS can be mitigated, at least in part, by demonstration of a large treatment effect on PFS. However, this uncertainty may not be completely addressed in this application due to the relatively small sample size of the POLO

trial and the observed PFS improvement, corresponding to a 3.6 months difference in median PFS demonstrated for olaparib.

The second issue relates to the limitations of the POLO trial. This application is supported by the results of a single randomized, placebo-controlled trial. As noted earlier, germline BRCA-mutated pancreatic cancer comprises a small subgroup of patients with pancreatic cancer, and the sample size of POLO is small at 154 patients. Additionally, although the trial had 80 percent power to show a 6-month improvement in median overall survival, it was not adequately powered to show a smaller improvement in overall survival.

An important consideration is that analyses of key secondary endpoints of POLO do not provide strong support that treatment with olaparib confers a clinical benefit to patients in the maintenance setting. Although the results for overall survival presented are not fully mature, the FDA statistical review team performed analyses indicating that the

likelihood of demonstrating an improvement in overall survival is low.

The POLO trial included assessment of measures of patient quality of life, which can support demonstration of clinical benefit. However, descriptive analyses of clinical outcome assessments did not demonstrate that treatment with olaparib improves cancer-related symptoms or other measures of patient quality of life. AstraZeneca does not plan on conducting an additional trial to further evaluate the benefit of olaparib for the proposed indication.

As part of the risk-benefit assessment for olaparib in patients with germline BRCA-mutated metastatic pancreatic cancer in the maintenance setting, FDA considers the totality of information, including the unmet medical need in patients with germline mutations in BRCA, and prior clinical experience with olaparib, including the demonstration of improvements in progression-free survival in patients with ovarian and breast cancer who have germline mutations in BRCA. Although no

new safety signals were identified, the toxicity of olaparib must also be considered in the context of the maintenance treatment setting, where a management alternative may include a drug-free interval.

Lastly, FDA considers the uncertainty regarding the potential benefit provided to patients, including whether the magnitude of prolongation in PFS conferred by olaparib is meaningful in light of the modest median improvement in progression-free survival; challenges to radiologic assessment of disease burden in pancreatic cancer; and the limitations of POLO, a single small-randomized trial that did not demonstrate statistically significant improvements on the other endpoints that may provide evidence of direct clinical benefit to patients.

FDA is seeking the committee's opinion on whether the risk-benefit relationship favors use of olaparib for the proposed indication. This concludes my remarks, and 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 interests and those based upon the outcome of the meeting.

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

speaking.

We'll now proceed with the applicant's presentations.

Applicant Presentation - Susan Galbraith

DR. GALBRAITH: Good morning, members of the advisory committee and FDA. My name is Susan Galbraith. I'm senior vice president and head of research and early development in oncology R&D at AstraZeneca. It's a pleasure to be here today to present to you the data in support of our supplemental NDA for olaparib as maintenance therapy in patients with germline BRCA-mutant pancreatic cancer.

Olaparib is the first PARP inhibitor approved, and it's currently registered for use in the U.S. for multiple indications, including ovarian cancer as both treatment and maintenance therapy and for the treatment of metastatic breast cancer. We're currently seeking regular approval in a third tumor type in an uncommon subgroup of pancreatic cancer with germline BRCA mutations.

Olaparib has a well-established safety

profile based on a large clinical trial safety database and 4 to 5 years of marketing experience. This slide illustrates the targeted mechanism of action of olaparib. Single-strand breaks in DNA are common, and even more common in cancer cells. When there is a single-strand break, poly ADP-ribose polymerase, or PARP, binds and triggers their repair.

Olaparib binds to and inhibits the catalytic function of PARP. It also traps PARP on the DNA, which results in double-strand breaks as shown on the right. Even a single double-strand break in a cell is potentially lethal. In a normal cell with proficient homologous recombination repair function, those double-strand breaks are repaired, and the cell survives. But in a tumor cell, with its homologous recombination repair deficient, or HRD, as is the case with BRCA mutations, these double strand breaks are repaired through an error-prone repair process, leading to accumulation of DNA damage and cell death.

This selective mechanism of killing of

BRCA-mutant cancer cells underpins the tolerability profile of olaparib and its suitability for maintenance therapy. Olaparib has much greater selectivity for BRCA-mutant cells compared to platinum chemotherapy, although its sensitivity to PARP inhibitors is highly correlated with sensitivity to platinum agents.

In a patient with a germline BRCA mutation, the normal cells shown in orange still have one functional copy of the BRCA gene and a homologous repair proficient. In contrast, tumor cells in these patients, shown in purple, have lost the function of the second BRCA allele, making them homologous repair deficient and sensitive to PARP inhibition.

Tumor cells that are homozygous for BRCA mutation are a thousand times more sensitive to cell killing with a PARP inhibitor versus the wild type or heterozygous BRCA-mutant cells. In contrast, BRCA-mutant tumor cells are only about 10-fold more sensitive to cell killing with platinum chemotherapy than wild type or

heterozygous cells. This means that an effective dose of platinum chemotherapy would kill a higher proportion of normal cells than an effective dose of olaparib. This cumulative normal cell killing limits the duration of platinum chemotherapy that can be tolerated clinically.

The clinical development of olaparib in germline BRCA-mutant pancreatic cancer began with a single arm phase 2 basket study known as Study 42. We showed a 22 percent objective response rate in this difficult-to-treat setting. Based on these promising results, we designed POLO, a randomized, placebo-controlled, phase 3 trial, investigating olaparib as maintenance therapy following one prior line of platinum-based chemotherapy.

The IND for the POLO trial was submitted in 2014. In discussions with the FDA about the reliability of assessment of progression-free survival in patients whose sole measurable disease is in the pancreas, we focused the patient population on metastatic disease. We also removed the planned interim analysis for PFS. We

retained PFS as the primary endpoint as a feasible and appropriate endpoint in this uncommon patient population.

The first subject was randomized in 2015. POLO is by far the largest study ever conducted in this small patient subgroup, and it took 4 years to screen 3,315 patients and randomize 154 patients. The sNDA was filed in June 2019 in parallel with the sPMA for the diagnostic. FDA granted priority review in August of this year.

A key topic for discussion at this ODAC is the relevance of maintenance therapy, which is commonly utilized in other tumor types, although not previously established in pancreatic cancer. In addition, we'll discuss the progression-free survival data from the polo trial and why it should support regular approval of olaparib maintenance therapy in this small patient subset.

Even when the intent is to treat progression with platinum-based chemotherapy, most patients cannot continue beyond 5 months because of the cumulative toxicity, as Dr. Kindler will explain.

Patients who stop chemotherapy are at high risk of recurrence or disease progression, which can be rapid, and they will inevitably require additional more toxic chemotherapy.

The goals of maintenance therapy are to delay progression, to delay the time to the next IV chemotherapy with its associated toxicities, and to maintain the patient's improved quality of life following effective first-line chemotherapy with the convenience of an oral medication.

Shown here is the proposed indication for which we're seeking regular approval. Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutant metastatic adenocarcinoma of the pancreas, whose disease has not progressed following a first-line, platinum-based chemotherapy. Patients will be selected for therapy based on an FDA-approved companion diagnostic for Lynparza. The approved dose in the U.S. for all indications is 300 milligrams given as two 150-milligram tablets twice daily.

Our presentation today will cover the following information:

1) the high unmet need in patients who've either completed first-line chemotherapy or cannot tolerate additional chemotherapy;

2) efficacy data showing olaparib maintenance therapy produced a statistically significant and clinically meaningful doubling of PFS and significantly delayed the time to the first subsequent therapy. The PFS analyses are robust and reliable, based on multiple sensitivity analyses. Olaparib also produced highly durable responses, including two complete responses, whilst maintaining patients' high baseline quality of life.

3) the safety data from POLO was both consistent with the known and well-characterized safety profile of olaparib and suitable for maintenance therapy in patients with germline BRCA-mutant pancreatic cancer. Based on all of these data, olaparib has demonstrated a positive risk-benefit profile in the proposed indication.

The agenda for the remainder of the sponsor presentation is as follows. Dr. Hedy Kinder from the University of Chicago will present an overview of the therapeutic landscape and the unmet need in germline BRCA-mutant pancreatic cancer.; Dr. Carsten Goessl will present the efficacy data from POLO; Dr. Mayur Patel will present the safety data; Dr. Margaret Tempero from the University of California San Francisco will provide her clinical perspective; and then I will summarize the benefit-risk profile. Dr. Larry Schwartz will be available to answer questions.

Thank you, and now I'd like to invite Dr. Kindler to the podium.

DR. HOFFMAN: Just one moment. Dr. Hawkins, would you just introduce yourself for the record, please?

DR. HAWKINS: Dr. Randy Hawkins, Charles Drew University.

Applicant Presentation - Hedy Kindler

DR. KINDLER: Thank you, Dr. Galbraith.

My name is Hedy Kindler. I'm a professor of

medicine at the University of Chicago. I was the co-principal investigator on the POLO trial. I will give you an overview of the disease background and unmet need in the treatment of BRCA-mutant metastatic pancreatic cancer. I am a paid consultant for AstraZeneca but have no financial interest in the outcome of this meeting.

Metastatic pancreatic cancer has a dismal prognosis, with the worst survival of any solid tumor. The 5-year survival rate of this disease is only 3 percent. About 57,000 Americans will be diagnosed with pancreatic cancer in 2019 and about 46,000 will die from it. As this figure illustrates, in the next year, pancreatic cancer is projected to become the second leading cause of cancer death in the United States. These abysmal statistics reflect the early distant spread of pancreatic cancer and the inadequacy of our current therapies.

At diagnosis, metastatic pancreatic cancer is a highly symptomatic disease. These patients often have significant pain that can only be

relieved with narcotics, which frequently cause constipation. Nausea from poor gastric emptying or narcotic use is very common, often requiring antiemetics.

These patients also experience significant weight loss due to early satiety and anorexia-cachexia. They frequently have pancreatic enzyme insufficiency, which causes further weight loss and bloating and requires enzyme supplementation, and they often experience depression and need antidepressants. Effective chemotherapy, however, can ameliorate many of these disease-related symptoms and improve their overall quality of life.

In unselected patients with metastatic pancreatic cancer, standard first-line treatment options include gemcitabine, gem-erlotinib, gem-nab-paclitaxel, and FOLFIRINOX. FOLFIRINOX, a platinum-based regimen, is quite active. In the pivotal study reported by Conroy, et al., FOLFIRINOX produced a median progression-free survival of 6.4 months from the start of

chemotherapy and a median overall survival of 11 months. In this study, only about 50 percent of patients were well enough to receive subsequent lines of therapy.

There have been many randomized trials investigating other chemotherapy drugs or novel targeted agents for this disease, and they have all been resoundingly negative. Thus, there have been no new frontline regimens approved for metastatic pancreatic cancer since 2012.

FOLFIRINOX is certainly effective, but it is also poorly tolerated. The side effects, particularly myelosuppression, fatigue, and neuropathy, are cumulative, and the neuropathy can be severe and irreversible. Intolerable sensory neuropathy is the most common reason that patients cannot continue on FOLFIRINOX. FOLFIRINOX is also a burden to patients who must wear an IV infusion pump at home and need frequent clinic visits for treatment, receiving growth factors and symptom monitoring.

In the pivotal FOLFIRINOX trial, although

the intention was to treat for 6 months, the median duration of treatment was 5 months or 10 2-week cycles due to disease progression or cumulative intolerable toxicity before disease progression. Grade 3-4 toxicities included neutropenia in nearly half of patients, fatigue in nearly a quarter, diarrhea in 13 percent, and sensory neuropathy in 9 percent.

About 1 in 15 patients with pancreatic cancer will have a germline BRCA1 and/or BRCA2 mutation, so this is an uncommon subpopulation. These mutations are increased in some ethnic groups and in people with a family history. Current clinical guidelines, both from ASCO and NCCN, recommend germline testing in pancreatic cancer patients. This type of testing can potentially save lives.

Patients with BRCA-mutated pancreatic cancer are particularly sensitive to platinum-based chemotherapy. When they are treated with a platinum-based regimen, they have a longer median survival, about 15 months, than patients who

receive non-platinum chemotherapy. This is longer than in the unselected pancreatic cancer population. Because of their longer survival, most gBRCA patients are able to receive multiple lines of subsequent therapy. NCCN guidelines recommend platinum-based chemotherapy in germline BRCA-mutated pancreatic cancer.

This slide illustrates the typical journey of a patient with gBRCA-mutant metastatic pancreatic cancer. These patients typically start with FOLFIRINOX. Some will have a planned stop after 6 months or they will most only receive about 5 months of therapy because cumulative toxicity limits how long they can stay on the regimen.

In the U.S., it is common to keep patients on chemotherapy until progression. However, cumulative neurotoxicity often becomes intolerable after about 4 months, and the oncologist will often drop the oxaliplatin and continue with FOLFIRI, and may later drop the irinotecan and continue with infusional 5-FU until progression. In reality, however, patients who respond to treatment or who

have stable disease will usually stop chemotherapy before progression, either as planned or because of toxicity. This allows them a short break from chemotherapy before resuming chemotherapy after progression.

When patients respond to chemotherapy, their disease-related symptoms typically decrease, and despite the toxicity associated with platinum chemotherapy, their health-related quality of life will often improve. After first progression, these patients usually receive additional platinum-based chemotherapy, depending on whether they are still considered platinum sensitive, and they may receive multiple lines of subsequent chemotherapy. As their disease continues to progress, disease-related symptoms will again increase, and they will experience renewed cumulative toxicities from chemotherapy. This contributes to a steady decline in their quality of life.

The goal of maintenance treatment after first-line, platinum-based chemotherapy is to delay progression, maintain the improved quality of life

achieved with chemotherapy, and delay the additional toxicity and burden of second-line, platinum-based chemotherapy. Maintenance therapy provides an additional treatment option. This strategy is most appropriate for patients who respond to chemotherapy and either stop treatment as planned or stop due to cumulative toxicity.

In summary, pancreatic cancer is a highly symptomatic disease with the briefest survival of any solid tumor. Germline BRCA-mutated pancreatic cancer is a unique subset associated with prolonged survival when treated with platinum-based chemotherapy regimens. But there remains a high unmet need because the cumulative toxicities associated with platinum regimens often limit the duration of chemotherapy and leave the patient at high risk for progression.

Effective maintenance therapy that can delay progression, maintain quality of life, and delay the need for additional chemotherapy remains an unmet need. Olaparib is a well-tolerated oral maintenance therapy that meets these criteria.

With that, I'm going to pass the podium on to Dr. Goessl.

Applicant Presentation - Carsten Goessl

DR. GOESSL: Thank you, Dr. Kindler.

My name is Carsten Goessl. I am the global development lead of olaparib across oncology indications at AstraZeneca. It is my pleasure to review the clinical development program for olaparib in pancreatic cancer and, in particular, the efficacy data from the phase 3 POLO trial.

The results of the multicohort Study 42 trial provided the rationale for developing olaparib as a maintenance therapy for germline BRCA-mutated metastatic pancreatic cancer. Study 42 included 23 metastatic pancreatic cancer patients with germline BRCA mutations. They received olaparib as a second-line or later therapy. We observed and objective response rate of 22 percent.

Patients whose tumors were nonresistant or not exposed to platinum-based chemotherapy had a good response rate and a prolonged progression-free

survival. Conversely, patients whose tumors were resistant to prior platinum did not respond. Therefore, our phase 3 POLO trial excluded patients who had progressed on the prior platinum regimen.

POLO is a well-conducted, randomized, double-blind placebo-controlled trial in adenocarcinoma of the pancreas in the maintenance setting. We screened 3,315 patients taken over 4 years to randomize 154 patients with a gBRCA mutation. In terms of screening, this is clearly the largest prospective study in pancreatic cancer ever undertaken.

Patients had received at least 16 weeks of platinum-based chemotherapy with no upper limit to ensure that patients have adequate platinum exposure, and they must not have progressed on chemotherapy. We randomized 154 patients in a 3 to 2 fashion. Thus, 92 patients were randomized to olaparib 300-milligram tablets twice daily and 62 patients to placebo.

The primary endpoint was progression-free survival by a blinded independent central review,

BICR, and we also performed the sensitivity analysis of progression-free survival by local investigator assessment. Overall survival was a key secondary endpoint. Other prespecified secondary efficacy endpoints included progression-free survival 2, which is a time to second progression or death; and then TFST, which is time to first subsequent therapy; overall response rate, including duration of response; and finally health-related, quality-of-life assessments.

We planned the primary PFS analysis at approximately 87 PFS events, and there is an IDMC monitoring the study for safety and futility. The study had 80 percent power to detect a statistically significant PFS benefit at a 5 percent significance level, assuming a hazard ratio of 0.54. The assumptions for median progression-free survival were 7.4 months in the olaparib arm and 4 months in the placebo arm.

The statistical analysis plan specified that we would only analyze OS if the PFS target was met

and there was adjustment protesting [indiscernible] overall survival twice. An interim OS analysis was to be conducted at the time of the final PFS analysis. A final OS analysis will be done when 106 test events have occurred.

We required a minimum of 16 weeks of first-line, platinum-based chemotherapy. Patients who had a response or stable disease to platinum chemotherapy, they're randomized within 4 to 6 weeks to either olaparib or placebo. Patients continued blinded maintenance treatment until disease progression. Afterwards, many patients went on to receive multiple subsequent lines of chemotherapy.

Progression-free survival was a primary endpoint. Patient-reported, health-related quality of life was also measured up to the time of progression. Very clinically relevant, secondary endpoint was time to first subsequent therapy because of the toxicity associated re-exposure to chemotherapy. We also evaluated progression-free survival 2, and finally overall survival. Note

that all endpoints were measured from randomization.

Fifty-nine percent of patients in the olaparib arm discontinued due to disease progression compared with 79 percent in the placebo arm. Discontinuations for other reasons were similar between arms. Notably, one sort of patients in the olaparib arm was still continuing on assigned study treatment at the data cutoff compared with only 13 percent in the placebo arm. We had a median follow-up for progression of 9 months in the olaparib arm and 4 months in the placebo arm.

Now, on to patients' baseline characteristics, median age was 57 years in both arms as expected for germline BRCA-mutant metastatic pancreatic cancer population. There were minor numerical differences between treatment groups, but none that would affect the outcome. We confirmed this in a multivariate analysis. Continuing with patients' characteristics, let me highlight some key factors.

More than 80 percent of first-line platinum chemotherapy was FOLFIRINOX in both arms. Half of patients in both arms had an objective response, that is PR or CR, on prior chemotherapy. The other half had stable disease as best response to first-line chemotherapy. As expected, metastases were found most often in the liver, followed by the lung, peritoneum, and other sites.

Here is a primary endpoint of the trial. It shows a statistically significant and clinically meaningful 47 percent reduction in the risk of disease progression or death with a corresponding hazard ratio of 0.53 and a p-value of 0.0038.

Median progression-free survival was 7.4 months in the olaparib arm. This is almost double as the progression free survival in the placebo, which was 3.8 months in line with expectations. Of note, a substantial proportion of patients in the olaparib arm remained free of progression beyond 2 years. This tail suggests that olaparib is associated with a prolonged benefit.

Consistently, at every prespecified landmark

time point, from 6 months onwards, the proportion of patients remaining free from progression or death was more than double in the olaparib arm compared with the placebo arm. You can see that more than 20 percent of olaparib patients were alive and free of progression at two years. This compared with only 10 percent in the placebo group.

To confirm the robustness of the primary outcome, we did various sensitivity analyses. We conducted a prespecified sensitivity analysis of PFS by investigator, and the results were nearly identical to the primary analysis by BICR. There's a hazard ratio of 0.51. As you can see, the Kaplan-Meier curves are very similar, and the rate of concordance between investigator and BICR was 82 percent.

Now, we recognize that measurement of lesions within the pancreas can be challenging, however, in POLO, we are confident that the radiologic assessments are both reliable and robust. To confirm this, we conducted additional sensitivity analyses of the PFS results. These

sensitivity analyses, based on BICR assessment, included exclusion of those patients who had target lesions only in the pancreas, and then exclusion of those patients who had progression only in the pancreas. And finally, we excluded any pancreatic lesion from the analysis.

As you can see, the hazard ratios remained in a tight range from 0.46 to 0.62. That's confirming that the primary PFS analysis by BICR is robust irrespective if pancreas lesions are included or excluded in the analysis. Consistent with a subgroup analysis performed by the FDA, our prespecified subgroup results favor olaparib with overlapping confidence intervals, and these results are in line with the primary analysis.

Thus, variability in the treatment effects in the subgroups is consistent with the random fluctuations. Note, the results remain comparable whether patients had an objective response or stable disease to prior platinum regimen.

Here's an interim analysis of overall survival. While the results numerically favor

olaparib with a hazard ratio of 0.91, this did not reach statistical significance. The median overall survival was 18.9 months in the olaparib arm versus 18.1 months in placebo.

In a larger study, this hazard ratio might translate to a 2-month improvement in median overall survival. We will have a final overall survival analysis at 106 events, which is expected to occur late next year. The conditional power is 9 percent to detect an overall survival difference at the final overall survival analysis.

Based on the information we have today about a comparatively long survival in the 6 percent gBRCA-mutated target population, we would have had to screen more than 30,000 patients and enroll more than 2,000 patients to detect a 3-month overall survival benefit. Because patients with BRCA mutations who receive platinum-based chemotherapy survive longer than the unselected pancreatic cancer population, there is a greater opportunity for subsequent therapies, which have a potential to dilute the overall survival results.

One sort of patients in the olaparib arm remained on study treatment at the data cutoff date and could not yet have received subsequent therapy compared to only 13 percent on placebo. Although there was an imbalance in the proportion of patients receiving subsequent therapy, there's 49 percent in the olaparib 74 percent in the placebo arm.

Time to the first subsequent cancer therapy is particularly relevant to patients due to the toxicities associated with reinitiation of chemotherapy. This analysis shows a hazard ratio of 0.50 with a median of 8.6 months in the olaparib arm. The placebo arm had a median of 5.7 months, and the curve has a tail similar to what we saw in the primary PFS analysis.

Objective response rate was determined in the 84 percent of patients who had measurable disease at study entry. We observed a 23 percent response rate in the olaparib arm, including 2 complete responses, compared with an 11.5 percent response rate in the placebo arm, which is likely a

carryover effect from chemotherapy.

The notion of carryover is suggested by the short time to onset in the placebo arm, depicted in the upper-right figure. Note, in the lower-right figure, the very durable responses in the olaparib arm with a median of over 2 years. PFS2 is a meaningful endpoint because it suggests that the benefits of olaparib extend beyond the first progression. Time to second progression or death is counted from randomization and is based on investigator assessment.

This analysis is not mature, the hazard ratio is 4.76, and it is not statistically significant. But you do see separation of the curves in favor of olaparib, starting at about 8 months.

We also evaluated health-related quality of life using several standard patient-reported outcome measures with global health-related quality of life as a main PRO endpoint of interest. Patients entered the POLO trial with high health-related, quality-of-life scores, 70 over

100 scale in both arms. Higher scores indicate better health-related quality of life, and a 10-point change from baseline was predefined as clinically meaningful.

The bar graph shows that olaparib treatment preserved overall health-related quality of life with no meaningful difference compared to placebo. This is relevant from the patient perspective, as olaparib prolongs progression-free survival with no apparent detriment on quality of life.

As outlined by Dr. Kindler before, pain is a frequent symptom of metastatic pancreatic cancer. Here are the results for the prespecified exploratory analysis for the time-to-pain progression. Olaparib appears to delay time-to-pain progression, which is a relevant benefit for patients. Median time-to-pain progression was 7.4 months in the olaparib arm versus 4.4 months in the placebo arm, with a corresponding hazard ratio of 0.7.

To summarize, POLO met its primary endpoint. It is a positive study demonstrating a

statistically significant and clinically meaningful 47 percent reduction in the risk of disease progression or death compared with placebo. POLO also demonstrated a meaningful benefit to patients in multiple key secondary endpoints.

Investigator-determined PFS results matched those by BICR. Olaparib delayed the time to subsequent chemotherapy by 50 percent, which is particularly relevant to patients due to the associated toxicities with the reinitiation of chemotherapy. The benefits of olaparib extend beyond the first progression as suggested by the PFS2 data.

The hazard ratio for overall survival was directionally favorable. Moreover, almost a quarter of patients on olaparib had an objective response, including 2 complete responses. Olaparib also yielded a very long duration of response, with a median of over 2 years. Importantly, all these benefits were achieved without evidence for a compromised health-related quality of life.

In conclusion, the totality of the evidence

supports
a meaningful clinical benefit of olaparib as maintenance therapy in patients with gBRCA-mutated metastatic pancreatic cancer. Dr. Mayur Patel will now present the safety findings from POLO. Thank you.

Applicant Presentation - Mayur Patel

DR. M. PATEL: Thank you, Dr. Goessl.

My name is Mayur Patel, and I'm the vice president of patient safety oncology at AstraZeneca. I will now review the safety data from the POLO trial, as well as the established safety profile of olaparib.

The safety profile is well characterized. As described earlier, olaparib is already approved in the maintenance and treatment settings in ovarian cancer and for the treatment of metastatic breast cancer. About 12,000 patients have received olaparib in a variety of solid tumors. Of these, over a thousand patients have received olaparib in registrational clinical trials in the maintenance setting. In addition, since 2014, there's been

more than 20,000 patient-years exposure to olaparib in a postmarketing setting.

The most commonly reported adverse reactions include anemia, nausea, vomiting, diarrhea, and fatigue/asthenia. These events are generally mild to moderate in nature. The safety profile of olaparib comes from 91 patients in the POLO study and a large supported pooled data set of 1329 patients who received the approved dose of olaparib in either the treatment or maintenance settings.

A majority of patients received a full dose of 300 milligrams twice daily throughout the study. This table shows the proportion of patients who are on the full dose in the top row. The rows below show the proportion of patients who had a dose reduction. The columns show the proportion of patients still on olaparib in 3-month intervals. Note, the end decreases of each time period as patients progress and stop olaparib treatment.

Throughout the study, the majority of patients were able to tolerate the full dose of olaparib. Consistent with the median PFS data,

exposure on the olaparib arm was approximately 1.6 times longer than in the placebo arm.

This table summarizes treatment-emergent adverse events in the POLO study. Over 90 percent of patients in both arms experienced an adverse event of any grade. About 40 percent of patients on olaparib and approximately a quarter of patients on placebo experienced a grade 3 or higher adverse event. Twenty-four percent of patients on olaparib and 15 percent of patients on placebo experienced a serious adverse event.

The relatively large number of placebo-treated patients experiencing either a high grade or a serious adverse event reflects a high burden of disease in this patient population. There were no treatment-emergent adverse events with a fatal outcome in either arm. After the 30-day follow-up period, 2 patients in the olaparib died from causes not considered to be due to disease progression by the reporting investigator; one from an unknown cause and the other due to refractory septic shock while receiving cisplatin

and gemcitabine as a subsequent therapy.

Dose interruptions and, if needed, dose reductions are the main strategies for toxicity management for olaparib. Around a third of patients had a dose interruption and 16 and a half percent had a dose reduction. These strategies were very effective at managing adverse events, as only 5 patients discontinued olaparib due to an adverse event.

This plot shows the most common all-grade adverse events with olaparib on the left and placebo on the right. Consistent with the known safety profile of olaparib, the most common adverse events were fatigue, gastrointestinal effects such as nausea, vomiting, diarrhea, and hematological effects such as anemia.

You will also see some disease-related events such as pain symptoms like abdominal pain and back pain, and also peripheral neuropathy, which is a residual effect from chemotherapy. Importantly, the vast majority of these events were grade 1 and resolved without the need for

intervention.

Moreover, the incidence of grade 3 or grade 4 adverse events was low. The most common grade 3/grade 4 adverse events were anemia and fatigue. Only 4 patients on olaparib experienced a grade 4 adverse event of any type. So what is the impact to patients? Despite the occurrence of adverse events, there were no clinically meaningful differences in health-related quality of life compared to placebo.

With the exception of anemia, SAEs are well balanced between the olaparib and placebo arms, and there were very few SAEs that reported in more than one patient. Six patients in the olaparib arm experienced SAEs of anemia, which is a class effect with PARP inhibitors. Anemia can be managed with dose interruptions as a first step, dose reduction for subsequent events, and standard supportive care methods. SAEs of anemia were transient, reversible, and did not lead to treatment discontinuation.

Only 5 patients discontinued olaparib due to

an adverse event, and the majority of these were single events. Myelodysplastic syndrome, acute myeloid leukemia, other new primary malignancies, and pneumonitis are adverse events of special interest for olaparib. These are kept under close scrutiny in all of our studies, but to date there is insufficient evidence to support a causal relationship with olaparib.

In POLO, there were no adverse events of MDS or AML in either arm, nor were there other new primary malignancies reported during the treatment period and during the end of the 30-day follow-up period. There were two new primary malignancies reported after the 30-day follow up period, both in the placebo arm, a rectal cancer and an ovarian cancer. Finally, there was one non-serious grade 1 asymptomatic event of pneumonitis in the olaparib arm, which was not associated with treatment discontinuation.

The safety profile of olaparib has been consistent across all studies in different tumor types. The most common adverse events in the

olaparib arm of POLO are shown on the left-hand side. The right-hand side shows the pooled data from 1329 patients treated with olaparib monotherapy such as the existing approved indication in ovarian cancer.

The median duration of exposure to olaparib in this pooled data set was 9 months, and over 20 percent of these patients received olaparib for more than 2 years. The incidence of the most common adverse events in POLO for both all-grade and grade 3/ grade 4 adverse events was consistent between the POLO study and the large pooled data set.

In summary, olaparib has a well-characterized safety profile and is well tolerated. The safety data from POLO was consistent with the data and its approved indications in ovarian and breast cancer. Therefore, the safety data supports the use of olaparib for the proposed indication for maintenance therapy in gBRCA-mutated metastatic pancreatic cancer.

Now, I'd like to invite Dr. Tempero to the podium.

Applicant Presentation - Margaret Tempero

DR. TEMPERO: Thank you, Dr. Patel.

My name is Margaret Tempero. I serve as director of the Pancreas Center at the university of California San Francisco. I'm here to provide my clinical perspective on the results of the POLO trial. I'm not being compensated for my time today, although my travel expenses are being covered by AstraZeneca, and I have no financial interest in the outcome of this meeting.

As you heard from Dr. Kindler, pancreatic cancer, especially when metastatic, is a very symptomatic disease. These patients are often in severe pain that requires narcotics for relief. Nausea is very common and often requires antiemetics. These patients experience a tremendous amount of weight loss and pancreatic insufficiency. Because of the latter problem, we usually start these patients on pancreatic enzymes to stabilize weight loss.

Finally, many patients are depressed and may require antidepressants, so even before we can start these patients on chemotherapy, they are dealing with a significant amount of polypharmacy just to control symptoms. When effective, chemotherapy can make a huge difference for patients, especially with respect to relieving cancer-related symptoms and minimizing the drugs needed to treat those symptoms. However, over time, cumulative toxicities eventually emerge.

Peripheral neuropathy is one of the most difficult of these side effects and is irreversible in some patients. When patients respond to first-line chemotherapy and have a chemotherapy holiday, they have an opportunity to recover from some of the side effects of chemotherapy. But once they progress, they are faced with the prospect of renewed side effects, particularly neurotoxicity and myelosuppression, along with the advancing burden of their disease.

Maintenance of response is a huge unmet need for patients with pancreatic cancer. Ideally, oral

maintenance therapy in this setting should delay the reemergence of cancer-related symptoms and give the patient freedom from the toxicities of chemotherapy while eliminating repeated visits to the infusion center or to the lab for monitoring.

Maintenance therapy is a paradigm shift. These graphs are based on what was observed in the POLO trial in patients who had an objective response or stable disease to first-line chemotherapy. Patients in the placebo arm had a break from chemotherapy for a median of only 3.8 months and went on to receive additional FOLFIRINOX or gemcitabine and nab-paclitaxel.

In contrast, patients on the olaparib arm had a median of 7.4 months before they progressed and 8.6 months before they received subsequent chemotherapy. That delay is very meaningful to patients and represents a period of time when they can be treated at home with a well-tolerated oral therapy and spend time with their families rather than traveling back and forth to the clinic for treatment. It also adds time to recover more

completely from the cumulative side effects of chemotherapy.

In summary, prolonging progression-free survival is meaningful to patients. The POLO trial met its primary endpoint, demonstrating a clinically meaningful 47 percent reduction in the risk of disease progression or death. The POLO trial may not establish an overall survival benefit in the maintenance setting, but a trial powered for overall survival may not have been feasible, and if actually conducted, would have delayed access to olaparib for this group of patients.

Based on the POLO data, I believe that olaparib is a safe and effective treatment for BRCA-mutated pancreatic cancer patients, and exceptional durable responses were observed that are transformative to patients.

Now, I'd like to invite Dr. Galbraith back to the podium.

Applicant Presentation - Susan Galbraith

DR. GALBRAITH: Thank you, Dr. Tempero.

You've heard from Dr. Kindler why germline

BRCA pancreatic cancer is an area of high unmet need. You've heard from Dr. Goessl and Dr. Tempero that in the POLO study, olaparib provided meaningful clinical benefit as seen by improvement across a range of clinical endpoints. I'd like to summarize why PFS is the right endpoint to use in this patient population and why the magnitude of benefit is clinically meaningful and can support regular approval.

We assert that progression-free survival is a meaningful endpoint in germline BRCA-mutant pancreatic cancer because of the biology of this disease. This is a unique subset. It's different from the general pancreatic cancer population. In this subset, PFS is still short, and patients return to multiple rounds of chemotherapy with accumulating toxicity and reducing benefit.

However, in contrast to unselected patients, the time from first progression to death is more prolonged when patients are treated with platinum-based chemotherapy. Therefore, further prolongation of progression-free survival can be

meaningful to these patients because it delays the time to the next toxic IV-administered chemotherapy.

Importantly, overall survival benefit is difficult to demonstrate in this population because the effect size might be diluted by multiple subsequent therapies, and a clinical trial powered for OS would not be feasible. Based on what we've observed in POLO, it would require us to screen over 30,000 patients and might take many years to complete.

POLO demonstrated a positive benefit-risk profile for olaparib. A PFS benefit with a hazard ratio of 0.53 is a meaningful improvement. Furthermore, with a median of 8.6 months to the first subsequent therapy, it means that up to half of a patient's remaining life expectancy of around 18 months could be chemotherapy free.

Throughout, sensitivity analyses have shown the effects observed in POLO to be robust. We observed highly durable responses with a median duration of response of more than 2 years and

prolonged progression-free survival. The PFS benefit is further supported by multiple clinical endpoints, including overall response rate, the time to first subsequent therapy, the time to second progression, and maintenance of patient-reported outcomes.

Olaparib is well tolerated with a safety profile suitable for maintenance therapy. Finally, the totality benefit we observed in POLO is consistent with the totality of benefit we've seen with olaparib across multiple BRCA-mutant tumor types, including ovarian cancer, breast cancer, and most recently, prostate cancer.

POLO is practice changing. Experts in the treatments of pancreatic cancer have updated clinical practice guidelines to include the option of olaparib maintenance therapy in patients with BRCA-mutant metastatic pancreatic adenocarcinoma. Thank you for your attention. This concludes the sponsor presentation.

DR. HOFFMAN: Thank you very much.

We will now proceed with the presentation

from the FDA.

FDA Presentation - Naomi Horiba

DR. HORIBA: Good morning. My name is Naomi Horiba, and I'm a medical oncologist and the clinical reviewer for the supplemental new drug application 208558 for olaparib submitted by AstraZeneca, referred to as the applicant for the remainder of the presentation. This slide lists the names of the members of the FDA team for this application, and my presentation reflects their collective input.

I will begin with a brief overview of the results from the POLO trial. I will then present the issues that serve as the basis for referring this application to the advisory committee, including the uncertainty regarding the magnitude of improvement in progression-free survival, or PFS, conferred by olaparib, and limitations of the POLO trial, the single, randomized-controlled trial supporting this application. Finally, I will provide a summary, followed by the voting question for the committee.

In the next few slides, I will provide a brief overview of the results of POLO. As a reminder, the POLO study provides the primary evidence to support the evaluation of safety and efficacy for this application. The design of POLO is shown here. Eligible patients were those who had not had progression following at least 16 weeks of a first-line, platinum-based chemotherapy, and therefore were a patient population with a more favorable prognosis as compared to a population of patients who experienced disease progression following first-line treatment. In total, 154 patients were randomized.

In general, FDA agrees with the applicant's presentation of the results for the final analysis of the primary endpoint of PFS and the interim analysis of the key secondary endpoint of overall survival or OS. POLO demonstrated a statistically significant improvement in PFS for olaparib, with a hazard ratio of 0.53, translating to a median improvement in PFS of 3.6 months.

The Kaplan-Meier curves for PFS are shown

here. At the time that the curves begin to separate, after 40 percent of events had occurred, FDA notes that 53, or less than 58 percent, of the patients in the olaparib arm, and 23, or 37 percent of patients, in the placebo arm were at risk of experiencing a PFS event, reflecting the small number of patients who contributed to the observed difference in PFS.

I will now present the analysis of the safety of olaparib important to the risk-benefit assessment. In general, FDA does not object to the applicant's presentation of the safety results of the POLO trial and agrees that the safety profile of olaparib observed in POLO is similar to the known safety profile of olaparib and that no new safety signals were identified in this application.

Selected toxicities observed more frequently in the olaparib arm of POLO are shown here. Of note, 45 percent of patients on the olaparib arm experienced fatigue, including 4.4 percent of patients with grade 3 fatigue. Additional toxicities observed at a higher frequency in the

olaparib arm compared to placebo were primarily gastrointestinal in nature. Anemia, decreased appetite, and rash were also observed with a higher frequency in the olaparib arm.

The pattern of serious adverse events that occurred on the olaparib arm in POLO was consistent with the profile observed in patients with ovarian and breast cancer, diseases for which olaparib is approved. A moderately higher rate of serious adverse events was observed in the olaparib arm compared to the placebo arm, with 24 percent of patients treated with olaparib having a serious adverse event as compared to 15 percent in the placebo arm. Overall, patients receiving olaparib experienced an increase in toxicity compared to those receiving placebo, particularly with respect to gastrointestinal toxicities and fatigue.

I will now discuss the two issues for which FDA seeks the input of the committee. The first issue is the uncertainty about the true magnitude of the improvement in PFS. The second issue relates to limitations of the POLO trial. I will

begin by discussing the issue of uncertainty about the magnitude of improvement in PFS conferred by olaparib.

FDA has accepted PFS as an intermediate endpoint reasonably likely to predict clinical benefit to support accelerated approval for solid tumor indications other than pancreatic cancer when the magnitude of PFS improvement is clinically meaningful and the overall risk-benefit assessment is favorable. Additionally, for some cancer types, FDA has considered demonstration of a statistically robust large improvement in PFS to be a direct measure of clinical benefit that supports traditional approval, typically for treatment of cancers with a longer life expectancy.

One advantage of PFS is that it reflects tumor growth and can be assessed before the determination of a survival benefit, and in clinical settings where the life expectancy of the disease is longer, this endpoint may be appropriate. Another advantage of PFS is that the results are not confounded by subsequent treatment.

The limitations of this endpoint include that it is based on radiographic imaging assessment and can thus be influenced by the timing of assessments and requires an accurate and unbiased assessment of tumor size and results.

Additionally, an improvement in PFS may not necessarily reflect a clinically meaningful benefit to patients, particularly when small in magnitude.

FDA notes that the 95 percent confidence interval for the observed point estimate for the hazard ratio for PFS is relatively wide, ranging from 0.35 to 0.81. The estimated improvement in median PFS ranges from 9 days to 7.3 months, reflecting a degree of uncertainty of the magnitude of PFS benefit conferred by olaparib.

As noted in FDA's 2018 guidance for industry on clinical trial endpoints for approval of cancer drugs and biologics, the accuracy and the ability to measure tumors can differ among tumor settings and can be imprecise in locations where there is a lack of a demarcated margin such as the peritoneum and pancreas. Challenges with imaging assessment

of pancreatic cancer across various settings have been described in published articles. For example, one meta-analysis published in 2018 concluded that CT has only a moderate diagnostic accuracy in the detection of recurrent disease.

This slide shows the results of the analysis for overall response rate, or ORR, in POLO. As a reminder, ORR was assessed according to RECIST 1.1 and by blinded independent central review. As shown, the overall response rate was approximately 20 percent in patients randomized to olaparib and approximately 10 percent in patients randomized to placebo.

FDA noted the response rate in the placebo arm, and therefore performed an analysis of time to first response in the placebo arm to assess whether it might reflect a delayed response to prior chemotherapy. FDA determined that for at least some patients, this was unlikely. For example, the initial radiologic assessment of overall response occurred over a range, from week 7 to week 31. The finding of tumor responses in the placebo arm,

therefore, may reflect the limitations in the radiographic assessment of tumor size in pancreatic cancer.

FDA performed an analysis of the sites of disease progression to evaluate the extent to which PFS was diagnosed at sites in which radiologic assessment of disease burden is recognized to be challenging in pancreatic cancer. Because the radiographic accuracy in identifying progression would be expected to be high in patients whose disease had progressed simultaneously in multiple sites, this assessment focused on patients whose progression was reported in a single anatomic site.

In POLO, 60 patients in the olaparib arm and 44 in the placebo arm experienced disease progression. Of these, approximately 60 percent were determined to have progressed based on findings in a single anatomic site. Overall, approximately 20 percent of patients with disease progression were diagnosed with progression based solely on findings in the pancreas or peritoneum, sites which are recognized to be difficult to

assess radiographically, adding uncertainty about the accuracy of assessing PFS in these patients.

Although FDA has approved drugs for cancers such as ovarian cancer that may be difficult to assess radiologically, based upon demonstration of an improvement in PFS, in general, the observed differences were large enough in magnitude to overcome potential uncertainty regarding the precision of radiologic assessment of PFS. In POLO, the observed improvement in PFS, corresponding to the 3.6-month improvement in the olaparib arm, may not be large enough to adequately mitigate the uncertainty.

I will now discuss the limitations of the POLO trial. The first limitation relates to the small sample size of the POLO trial. As a reminder, the efficacy population in POLO consists of 154 patients. POLO was designed to have 80 percent power to detect a hazard ratio of 0.57 for OS. Based on occurrence of 106 events, assuming a median OS of 8 months in the placebo arm and 14 months in the olaparib arm, the prespecified

sample size did not provide adequate power to show a more modest improvement in survival.

In general, randomization helps to ensure a balance in known and unknown prognostic factors that can influence study results. FDA agrees with the applicant that the known baseline demographic in tumor characteristics in POLO were generally similar. However, imbalances in unknown prognostic factors that impact patient prognosis may exist, and given the small sample size of this trial, it is uncertain whether randomization achieved a balance in other factors that can influence patient outcomes.

For example, the reasons for discontinuation of first-line treatment were not captured and CA 19-19 levels were not collected at baseline or during treatment. These uncertainties add to the challenge of interpreting the results of POLO.

As a reminder, prior approvals for pancreatic cancer have been based on or supported by a statistically significant difference in OS. As previously stated, POLO was designed with

adequate power to demonstrate a median OS difference of 6 months. As shown here, the interim analysis of POLO, which was performed following occurrence of 67 percent of the planned events and was therefore fairly mature, did not show a statistically significant difference in OS between the olaparib and placebo arms.

Although crossover and post-progression therapy can complicate the ability to demonstrate a difference in survival, crossover was not permitted in POLO, and only one patient on the olaparib arm and 9 patients, or 15 percent, on the placebo arm received subsequent therapy with a PARP inhibitor.

Here are the Kaplan-Meier curves for OS. As shown here, there is no clear separation between the Kaplan-Meier curves for OS in the olaparib and placebo arms. Based on FDA's calculation, the probability of the final OS analysis, showing a significant difference based on conditional or predictive power, is low and ranges from 5 to 16 percent. The applicant has no plans to conduct any additional studies to further evaluate the effect

of olaparib on overall survival.

The applicant conducted several analyses related to health-related quality of life, and concluded the treatment with olaparib maintains health-related quality of life and appears to prolong time to worsening of pain. FDA does not agree with the conclusions for several reasons.

The analyses were descriptive. Because there was no prespecified plan to adjust for multiplicity, FDA considers the reported p-values to be nominal and uninterpretable. Low patient numbers also preclude a reliable comparison between treatment arms. Additionally, POLO was not designed to demonstrate maintenance of health-related quality of life. FDA also notes that the descriptive analyses of the QLQ-C30 pain domain and QLQ-PAN26 26 pancreatic pain domain did not show a treatment effect for olaparib.

The POLO trial included prespecified analyses of time to first subsequent therapy, or death, or TFST, as a secondary endpoint. FDA does not consider this analysis of TFST to be a

meaningful efficacy measure given that the comparator in POLO was placebo, and patients randomized to olaparib received inactive drug with its associated toxicities. FDA further notes that this analysis was not controlled for multiplicity.

I will now summarize the issues to consider when evaluating the risk-benefit relationship for use of olaparib in the first-line maintenance setting in patients with metastatic pancreatic cancer harboring a germline mutation in BRCA.

When considering the risk-benefit relationship for the use of olaparib as maintenance treatment, there are several factors to consider. First, there is an unmet medical need for new safe and effective treatments for patients with gBRCA-mutated metastatic pancreatic cancer. In addition, the effectiveness of olaparib has been demonstrated for multiple indications, including for patients with gBRCA-mutated cancers.

Although no new safety signals were identified in POLO, the toxicities of olaparib, including fatigue, gastrointestinal toxicities,

anemia, decreased appetite, and rash, should be considered in the context of the maintenance setting where a management alternative may include a drug-free interval.

Finally, there is uncertainty regarding the potential benefit conferred by olaparib to patients given the challenges related to radiologic assessment of pancreatic cancer and the small sample size of POLO. In the absence of improvement in survival or other measure of clinical benefit, it is also unclear whether the magnitude of progression-free survival observed in POLO is clinically meaningful in this patient population.

FDA requests that the committee answer the following question. Is the risk-benefit assessment for olaparib as a maintenance therapy in patients with gBRCA-mutated pancreatic cancer favorable? This concludes FDA's presentation. Thank you.

Clarifying Questions to Presenters

DR. HOFFMAN: Thank you very much.

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 presenter.

DR. HOTAKI: Also just try to get my attention so I can make a running list. If you have a follow-on theme that we want to continue, just change your card like this, so we can keep with themes.

DR. HOFFMAN: Please?

DR. SUNG: Anthony Sung, Duke university. Would the sponsor please pull up, let's see here, CE-13? Looking at the patients who are older than 65 years, which is about a third of the patients in the study, there's not even a trend to a favorable progression-free survival in this population.

Would the sponsors please elaborate on why they think this is the case and if there's a biological difference between these age groups, or if there are issues with regard to older patients not being able to tolerate this drug?

DR. GALBRAITH: Given the number of baseline characteristics that were analyzed in this forest plot, you would expect some random variation, and

we did perform a global interaction test, which was not significant for any of these variations. So we think this is representative of the total population.

Furthermore, when you look at a subgroup of patients who are over 65, those patients had no difference in the tolerability profile and overall to olaparib. If you look at the subgroup that had long-term, progression-free survival on olaparib, there were 9 of 92 patients randomized to olaparib who remained on drug for 3 years or more. And of the 9 patients, 3 of those were more than 65 that were on for 3 years or more.

Of the 18 patients on olaparib who achieved an objective response who are more than 65, we contend that the patients who are more than 65 do derive benefit from olaparib and should be included in the overall population considered for approval.

DR. SUNG: So you gave examples of some patients who are older than 65 deriving benefit, but, again, I fail to be convinced that the overall population that are older than 65 derive benefit.

DR. GALBRAITH: I'd like to invite Dr. Hedy Kindler to make comments about the patient population included in POLO on the representation of more elderly patient population.

Dr. Kindler? Dr. Locker, perhaps?

DR. LOCKER: Gershon Locker, global clinical lead, AstraZeneca. If you look at the patients who had greater than 2 years on olaparib, you can see, again, that there were 3 patients who were over 65; so that is 3 of 28 patients over 65 who were on drug 2 years or more. If you look at the total number of patients who were randomized to olaparib, which is 92, it's 9 over 92.

So we can see no difference here, and the same goes for those patients who are now on for 3 years. The percent of patients who get long-term benefit is no different in the older group of patients than in the younger. So the issue is not older patients; the issue is the overall results. They do about the same and, again, the question is whether in multiple subset analyses, you're not likely to find one where it looks a little

different from all the others.

DR. HOFFMAN: Dr. Klepin?

DR. KLEPIN: Yes, thank you. I was just going to follow up on the second part of that question. Heidi Klepin from Wake Forest. Sorry.

Would you be able to show us any data using the age breakdown, 65 and above or below, and the adverse events, just so that we can see those numbers? I don't know if I saw those earlier.

DR. GALBRAITH: I'd like to invite Dr. Mayur Patel to talk about the adverse event rate in the older population.

Dr. Patel?

DR. M. PATEL: Given the small number of patients, we didn't look at the adverse events specifically in this group. But what you can see from this slide is that the adverse event rates between the older and the younger were similar. The only difference that you see in this category table is that patients that were older than 65 actually had fewer number of reductions, but the number of SAEs, those leading to the interruption

and discontinuations were largely similar between the patient populations.

DR. HOFFMAN: Dr. Halabi, do you have a follow-up for that?

DR. HALABI: Yes, I do. Actually, I was wondering if you looked at the other cutoff points for the age besides greater than 65 for both the PFS and the adverse event.

DR. GALBRAITH: I don't believe we've looked at different cutoff points, but should the FDA be interested in that, I can provide that data later.

DR. HALABI: Thank you.

DR. HOFFMAN: Dr. Hawkins?

DR. HAWKINS: Randy Hawkins, Charles Drew. There seems to be a difference, unless I misunderstood, in the interpretation of the quality-of-life results between FDA and the applicant. Did I hear clearly that FDA felt quality of life improvement was not significantly different or improved compared to the applicant?

DR. GALBRAITH: The health-related quality-of-life data that Dr. Goessl presented

shows that that was maintained from baseline. I'd like to invite Dr. Nikunj Patel to put that into that context for this study.

Dr. Patel?

DR. N. PATEL: Nikunj Patel, AstraZeneca, patient-reported outcomes. As Dr. Goessl mentioned in his presentations, the secondary endpoint in this trial was a global health-related quality-of-life mean change from baseline. Let me share patients' experience prior to POLO and once patients got on POLO.

Here, we're looking at average global quality-of-life score from the QLQ-C30 questionnaire. On the left side, you're looking at the PRODIGE4 Trial, which is a trial that established FOLFIRINOX as your first-line therapy. As you can see here, on the global score in the red circle, patients started out with a lower quality-of-life score at baseline, and they get better as they respond to the FOLFIRINOX therapy.

Now, in POLO, we enrolled these patients who responded to prior platinum therapy. These are the

patients who had PR. These are patients who had CR and stable disease. The baseline scores are almost similar to a general population. So we're not expecting these patients to get better, but what we do expect are these patients to get worse, and that did not happen throughout olaparib therapy. These patients remained active. They continued to maintain their baseline quality-of-life scores. They continued to participate in daily activities, and we believe, overall, that quality of life was maintained with no meaningful difference compared to placebo, which is a meaningful outcome for patients.

DR. HAWKINS: Thank you. Could FDA clarify its interpretation of the quality-of-life results?

DR. DONOGHUE: Hi. This is Martha Donoghue. Thank you for the question. There were several health-related, quality-of-life analyses that were performed, and we have several reasons for our statement that we disagree that there was a demonstration of improvement in health-related quality of life or maintenance of health-related

quality of life, actually.

We agree in principle that if you can demonstrate that treatment with a drug maintains patient quality of life, then that could be considered a benefit to patients. However, the trial wasn't designed to show that olaparib is going to maintain quality of life. What they appear to show with the descriptive analyses is that health-related quality of life doesn't appear to be much different between placebo and olaparib arms, which is different than actually saying that treatment with the drug results in maintenance of quality of life since it appears, at least in a descriptive level, that there aren't any major differences between the two arms.

So that's point number one. The second relates to lack of control for multiplicity. As you conduct multiple analyses, you're likely to see favorable trends in one analysis or another, and when you have lack of control for multiplicity, then the analyses have to be interpreted with caution.

We would also note, although not presented here, that many of the analyses, looking at time to clinically meaningful deterioration or time to clinically meaningful worsening in pain, even when you look at the p-values on a nominal basis, they did not approach statistical significance. So I think it limits our ability to infer one way or the other about whether olaparib improves quality of life.

DR. HOFFMAN: I have a question for probably Dr. Goessl. I think you noted that 9 patients from the placebo arm got olaparib after progression. Could one interpret that as a question of whether it's early olaparib versus later olaparib that makes the difference here, or is the lack of difference in overall survival because even though crossover wasn't specifically part of the trial, nonetheless, 9 people did get olaparib, and then whatever advantage they might have gained from that might have offset the difference?

DR. GALBRAITH: So a couple of points; one, as Dr. Goessl already presented, 33 percent of

patients at the time of data cutoff remained on olaparib, so hadn't yet had chance to get on to a second-line therapy. Further, it's not just PARP inhibition in the subsequent line that might affect and dilute the effect on overall survival, but further platinum-based chemotherapy, which the majority of patients did receive, could also have a similar effect. As Dr. Goessl noted, there was an imbalance in that.

So I'd like to invite, actually, Dr. Locker to come up and just describe again the imbalance in those two arms from one of the core slides.

DR. LOCKER: Gershon Locker, global clinical lead. The numbers were actually small, so it's very difficult to detect effect of the subsequent PARP inhibition. We think that the more likely thing for confounding at this point in the study is the subsequent platinum therapy. More than half of the patients on a placebo arm who progressed received the platinum therapy. One-third of the patients on olaparib didn't progress and couldn't receive anything, and 42 percent, there was an

imbalance receiving platinum therapy on olaparib.

So, yes, to answer your question, we do think there is confounding, but we think the confounding is by platinum. I might also add the studies which show that treatment with platinum does markedly increase survival in gBRCA metastatic pancreas cancer was not line specific. Some of those patients received second- and third-line platinum, and it markedly prolonged their survival, the Golan study and some of the others. So we really do think that it's the subsequent platinum and subsequent chemo, which does confound.

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

DR. KULKE: I'm also intrigued by the issues regarding second-line chemotherapy as they pertain to the overall survival results, and was curious if there's any evidence in this study, or other studies, that would suggest potential differences in chemotherapy response or benefit in patients who have received prior olaparib.

DR. GALBRAITH: We did look at the response

to subsequent therapy in the POLO study, and the response rates were similar in both arms, as was the rate of stable disease in both arms to the second subsequent therapy. That is consistent with what we've observed in other trials with olaparib also.

DR. SUNG: Tony Sung from Duke, again. This is actually a follow-up question to the quality-of-life questions. I noticed in the sponsor document that they said that patients were not followed beyond the 30-day, post-progression visit in either arm. I just want to make sure that that statement is correct because it means, at least to me, that some time points, you're including quality-of-life data from patients who have progressed but others who have not progressed, and it's a little bit mixed. Also, this makes it hard to interpret quality of life in patients who have maintained on maintenance therapy versus those who have started second-line therapy.

Can such a comparison be made?

DR. GALBRAITH: I'd like to invite

Dr. Nikunj Patel to provide further details. As he's coming to the podium, we did collect quality of life through to the time of progression and 30 days after, and Dr. Patel could show those data.

DR. N. PATEL: Nikunj Patel, AstraZeneca, patient-reported outcomes. That's correct. We did not collect data beyond 30-day progression. Let me show you what we have.

Here on this slide, we are showing the change from baseline in global, health-related, quality-of-life score at the end of treatment and the 30-day post follow-up. Again, this is after patient progressed. Regardless of which arm you're in, the blue bar going down or gray bar going down, meaning your quality of life is declining, it doesn't matter which arm you're in, your quality of life starts declining once you've progressed. These data are reflecting the PFS benefit that patients are receiving while remaining on therapy.

So if you're a patient on a placebo, your chance of getting to decline in quality of life is much sooner as you're progressing much faster, as

opposed to if you're a patient on olaparib, which is keeping you without disease progression significantly longer compared to placebo.

DR. SUNG: Just a follow-up. I guess the part that I'm having trouble understanding, as I understand the sponsor's argument, by keeping patients from having to start a second-line therapy for about 3 months, they may have better quality of life, but you don't actually have quality-of-life data to support that.

DR. GALBRAITH: No, we haven't data during the period where people are on the second-line chemotherapy. As Dr. Patel just showed, though, at the time when they are 30 days post-progression, you are starting to see a deterioration in quality of life, which gets to that clinically meaningful level. The numbers are small, as the FDA has noted.

DR. HOFFMAN: Dr. Halabi, did you have a follow-up for this?

DR. HALABI: No. Susan Halabi, Duke University. I have two questions to the sponsor

and one to the FDA. The first one is a follow-up to my earlier question regarding the age. The sponsor did mention that they did an analysis, age by treatment interaction, and it was not statistically significant. But this is expected because the number of events in this analysis is only 104, and the study was not designed to do that.

So the question really here is for the FDA. If age -- and we recognize that age is critical and valuable here because there was an imbalance in randomization, and we don't have data on age. How can we make a determination on the sensitivity analysis, whether different cutpoints may be robust or not? I mean, can you mandate this analysis to be provided? Because this information is missing, so I'm not sure if the FDA looked at this at different cutpoints.

DR. FASHOYIN-AJE: Our review of this application is ongoing. I think, though, the one thing I will say is that the numbers are so small and the subsets are so small that it's hard to

conclude there is detriment in effect, in the older patient population. But we are still reviewing some aspects of this application and wanted to focus on the key main issues that are of concern to us.

DR. HALABI: Okay. And to follow up --

DR. PAZDUR: Here again, we're going after exploratory analyses of exploratory analyses, so to speak, and obviously they don't have adequate statistical methodology to draw any conclusions regarding these; so these are simply hypothesis generating.

DR. HALABI: Yes, absolutely. I do recognize that. A follow-up to that, since, FDA, you mentioned that you're still looking at the data, is it legitimate to ask if there is updated data? Because the cutoff point was earlier in 2019. So is it a legitimate question to ask the sponsor to present updated data?

DR. FASHOYIN-AJE: I think we defer to the committee to make that determination as to whether or not you'd like to ask for additional data. As I

mentioned, we are still reviewing this application, so, again, as Dr. Pazdur mentioned, these are exploratory analyses and, really, they're pointing to potential signals, but it's hard to say anything conclusive about it.

DR. HALABI: Yes, absolutely. Then coming back to the other question, it has to do with slide CE-15 and CE-16. There were multiple lines of subsequent therapies that may dilute overall survival. I was wondering if the sponsor had performed different analyses that take into account subsequent therapy such as rank preserving structural failure or inverse probability, censor weighting, and if they could share those results with us.

DR. GALBRAITH: Yes, we have performed those data. I'd like to invite Dr. Nigel Baker to address that question.

DR. BAKER: Nigel Baker, biostatistician, AstraZeneca. If I could make a comment about the age group analysis, something that hasn't been mentioned yet, we've done quite a lot of

multivariate methods, including adding age into the model, along with treatment, and that leads to a result that is entirely consistent with the primary analysis

Switching to our analyses of taking into account subsequent therapies, yes, we have performed a rank preserving structural failure time model, and the results can be seen on this slide. The first row here shows the result of the interim analysis and has a ratio 0.91, as you've seen before. Then when we try and take into account the effect of that subsequent PARP therapy, you can see there is a very slight reduction in the hazard ratio, but I don't think anything that's of clinical relevance.

We did something slightly different, which was to exclude sites where any crossovers had occurred by excluding sites that maintain the randomization and less biased results. There again, we can see a slight reduction in the hazard ratio, so things are moving in the right direction but not a massively important impact.

Regarding follow-up data, I would just remind the committee that we have an alpha spending plan on overall survival, so if we were to supply an extra analysis of OS, we would need to take that into account, and there would need to be some discussion with the FDA about that.

DR. HOFFMAN: Did you have a follow-up, Dr. Kraus, to that?

DR. KRAUS: Yes, and it's just the question of measurability and lesions, which is one of the questions for discussion. The sponsor presented several sensitivity analyses, but I wanted to ask the sponsor and FDA if there were additional sensitivity analyses, other than those presented that, say, raise concern about the robustness. Usually a 0.5 is a pretty nice hazard ratio in the scheme of oncology studies, but I understand the concern, but usually that's gone after with sensitivity analysis of various sorts.

So I'm just wondering if there's additional granularity there that could be brought to bear or disagreement around sensitivity analysis or not,

because it looked like a number were done that supported consistency of effect.

DR. GALBRAITH: As Dr. Goessl described, we have done sensitivity analyses, first of all, primarily and comparing with the BICR analysis with the investigator analysis, which showed consistency, and then excluding various pancreatic lesions.

What I'd like to do is invite Dr. Larry Schwartz who can provide some context because he also had an opportunity to review the data from the POLO study.

Dr. Schwartz?

DR. SCHWARTZ: Thanks. My name is Larry Schwartz. I'm a diagnostic radiologist at Columbia University, College of Physicians and Surgeons. I'm also a busy practicing hepatobiliary radiologist, as well, for the past 25 years; so as such, I've actually reviewed thousands of patients and patient scans with pancreatic cancer. I'm an unpaid consultant to AstraZeneca, and also of note, I did not participate either as a site radiologist

or as part of the independent review, but I did review selected cases in this and the results in totality.

In general, I do believe the robustness of the progression-free survival analysis in this case. In general, primary pancreas lesions are difficult to measure, but especially in the setting of getting an absolute size, or seeing about its resectability, or the ability to resect relative to surrounding vessels.

In this case, as was noted and was actually a very elegant subanalysis by the FDA about the sites of metastatic disease, clearly when we're dealing with liver, lymph nodes, lung, that's like any other solid tumor, really, so I think that everybody accepts that.

With regard to the pancreas and the peritoneum, those are generally sites that can be considered more difficult to measure. These were all very good quality, contrast-enhanced CT scans generally with thin sections. I reviewed all the pancreas primary progression cases, in a

non-blinded way, though, and actually agreed with them. But what's even more interesting to note is that in the olaparib arm, 6 out of the 8 of those were deemed to be target lesions, and I would concur with those.

So those were actually primary pancreas or pancreatic lesions that the independent reviewers agreed were measurable in that they could call them target disease rather than just non-target disease.

In the experimental arm as well, for those patients with peritoneal disease, I did not review those, but I would note that 3 out of the 4 of those patients were deemed progressive based not on the growth of the peritoneal disease, either target or non-target, but actually on the presence of new peritoneal disease in other quadrants. So I would consider that to be very robust, as well, the identification of new lesions.

The other kind of overarching issue here is that the magnitude of the progression when it occurs was quite dramatic, and I think, unlike in other primary tumors as noted in the FDA guidance,

overrides the lack of precision in measuring. For instance, in the pancreas, the overall magnitude of measurement was about 1.5 centimeters to 5 centimeter growth when the progression actually occurred, and I think that that's within the precision.

If I may, I'd just like to show two imaging examples. This was one of the pancreas primary target lesions, in the tail, near the spleen of the pancreas, at baseline, measuring roughly 3.6 centimeters, and then at week 32, 6 centimeters. I think while the measurements we could maybe debate a millimeter or two, I think it was relatively straightforward to call this type of lesion. You also notice that this is a very good quality contrast IV and oral enhanced scan.

Next example, please. This is actually a non-target lesion. You see the texture difference at baseline, and I would agree that's a difficult lesion both to detect, and I agree that this would be considered non-target because of the inability to detect. But using the RECIST phraseology of

clear unequivocal progression of non-target disease, I think that that actually fits that, as well as in this patient, there was actually a new lesion, and I just show this example to illustrate both.

DR. HOFFMAN: Dr. Reidy?

DR. REIDY: Sorry. If we could just, again, go back to CE-15. My question to the sponsor was that only 49 percent of the patients on the olaparib arm were able to go on to subsequent therapy versus three-quarters of the patients on the placebo arm; and if you looked into the data as to why that may be, and if toxicities from the olaparib played a role in that?

DR. GALBRAITH: The biggest reason for the difference in that group is simply because there are 33 percent of patients that are still on the olaparib arm at the time of the data cutoff; so there aren't any differences in terms of the safety profile that leads to differences in the ability to take subsequent therapy. And as I noted, the response rate to subsequent therapy was similar in

both arms, as was the rate of stable disease.

DR. HOFFMAN: Dr. Sanoff?

DR. SANOFF: I'd like to ask a question about the clinical relevance of these results when you take them in the context of placebo-controlled trial here. You all showed the data on about a 5-month FOLFIRINOX treatment in first line in the Conroy trial, but I'm very curious to know if you have an understanding of what the standard of care is in the United States.

I know the NCCN guidelines say that a chemotherapy holiday is a reasonable thing to do. I don't actually necessarily agree with that. I think if you look at the Conroy trial, there was progression in about half of the people before 6 months, so I think that the idea that 5 months was the actual treatment course in that trial is a little bit misleading.

I think that actually a very relevant comparator arm would have been continued chemotherapy versus olaparib, and I'm very interested if you can comment on the clinical

relevance of these data, particularly given that when you reinstitute subsequent chemotherapy, we seem to see that the overall survival benefit of olaparib seems to perhaps go away.

DR. GALBRAITH: So just a couple of things to note. In order to be enrolled into the POLO study, patients had to have received a minimum of 16 weeks of platinum-based chemotherapy, but could go and continue on either FOLFIRI or 5-FU monotherapy, so that didn't exclude them from inclusion. Twenty percent of the patients in the POLO study were from the United States and Canada, and representative of treatment in this country.

I'd like to invite Dr. Margaret Tempero to give some context about the meaningfulness and the comparison also, potentially, with continuing chemotherapy versus maintenance and olaparib.

DR. TEMPERO: Thank you. Margaret Tempero, UCSF. The practice patterns really vary quite a bit across the country and in Europe versus the United States. In Europe, a chemotherapy holiday is probably the most common choice after about

6 months of therapy, assuming the therapy's been successful. In the U.S., it varies quite a bit, from chemotherapy holiday, as we do at UCSF, versus some ongoing form of chemotherapy, I think as Hedy pointed out, and maybe dropping drugs over time.

But I think it's very important to note the PANOPTIMOX study that was done, that was not done to show that maintenance therapy was equivalent or better, but it was done for a different reason. But those patients were randomized to FOLFIRINOX versus FOLFIRINOX, followed by maintenance 5-FU and leucovorin until progression, or just 6 months of FOLFIRINOX, and the overall survival and the progression-free survival were the same. That gave me quite a bit of confidence that actually doing a chemotherapy holiday in patients who are successfully treated was a safe thing to do.

DR. HOFFMAN: Dr. Klepin?

DR. KLEPIN: Yes. Thanks. Heidi Klepin from Wake Forest. This is a follow-up question to Dr. Reidy's regarding slide CE-15, I think, on the subsequent lines of therapy. Even when you account

for the patients who are still on treatment in the olaparib arm, it does seem as though there were still patients left over disproportionately in that arm who did not go on to a second line of therapy.

So I was wondering if you could at least show us the reasons for that because, in the back of my mind, it makes me wonder if there was some type of functional deterioration that might have been due to fatigue, for example. So it would be nice to see if there's some information around why those additional eligible patients didn't go on for treatment.

DR. GALBRAITH: I'd like to invite Dr. Carsten Goessl to answer to answer that question.

DR. GOESSL: Carsten Goessl, global development lead, AstraZeneca. The reasons of why a patient came on subsequent therapy or did not receive subsequent therapy, unfortunately, we did not capture that in the trial, so I cannot answer the question.

DR. HOFFMAN: Dr. Uldrick, do you have a

follow-up question?

DR. ULDRICK: I had a question for the FDA regarding the time to first subsequent therapy or death, and a difference in opinion between the FDA and the sponsor as to the relevance of this endpoint.

DR. DONOGHUE: Thanks for the question. We agree with the actual analyses performed, but we question the relevance of looking at that endpoint when you're comparing the time to first subsequent therapy in patients who received a placebo that doesn't have toxicity with olaparib, which of course does have toxicities. So we didn't consider that a fair comparison.

DR. ULDRICK: Thanks. I guess just a follow-up question for the sponsor, that I think one of the clinical benefits that is being suggested is that there's decreased toxicity by delaying second-line chemotherapy, and there is a schema showing decreased quality of life with second-line chemotherapy in the setting.

Is there evidence to suggest that this is

true? Because this was not measured in this study, and it makes it hard to analyze this study for this indication without measuring the quality of life in the second line.

DR. GALBRAITH: What I would like to suggest is that we can show the difference in the adverse event profile on olaparib versus the typical adverse event profile seen on the FOLFIRINOX chemotherapy. I'd like to invite Dr. Mayur Patel to give those details.

DR. M. PATEL: Mayur Patel, patient safety, AstraZeneca. You can see from this slide here, when you take the most common grade 3/grade 4 adverse events occurring greater than 5 percent on FOLFIRINOX therapy in the ACCORD 11 trial versus these high-grade events that were observed in olaparib, what you can clearly see is that the rate of neutropenia is significantly higher. Most of the neutropenia patients in FOLFIRINOX actually required a supportive therapy with CSF.

What you also see is that the vast majority of the events on FOLFIRINOX are much higher grade

than what you would expect, or what we observed in the actual POLO study.

DR. HOFFMAN: Dr. Cristofanilli?

DR. CRISTOFANILLI: Yes. It seems to me that this study actually demonstrated that taking a break, a holiday, is okay if patients have a sensitivity to treatment because I'm sure the overall survival in the control group was more than you expected because these patients seemed to maintain sensitivity to platinum compounds and platinum combinations.

The question would be, eventually, if you can take a PARP inhibitor between two chemotherapy treatments, would this improve survival? Obviously, I think this is going to take a longer time because you selected patients that are sensitive. Do you have any sense or do you have any data for the patients that do not achieve response but were with stable disease when they entered the study, if they had a superior benefit or not?

DR. GALBRAITH: As Dr. Goessl showed in the

core slides -- I'm looking at the forest plot from that -- there was a similar hazard ratio for effect on the benefit of olaparib regardless of whether patients achieved stable disease or partial response to the first-line, platinum-based chemotherapy. I can just show that in the forest plot again just to remind you.

Again, if patients had 16 weeks to 6 months, or more than 6 months of first-line, platinum-based chemotherapy, you can see the hazard ratios reflect the -- perhaps the most platinum-sensitive patients are more likely to respond to olaparib and gain further benefit. And again, that's consistent with the correlation that we see broadly across different tumor types, that platinum sensitivity correlates with PARP sensitivity.

DR. CRISTOFANILLI: So that would be the group that eventually gets overall survival benefit.

DR. GALBRAITH: I think just to put another bit of context on what it means for patients, potentially when they're on maintenance therapy,

I'd just invite Dr. Hedy Kindler to give her context about meaningfulness for patients.

DR. KINDLER: In my experience, patients really appreciate the chance to have a break from intravenous chemotherapy, and I think telling you about a patient of mine might put that into context.

This was a gentleman who watched his brother die of pancreatic cancer, so he knew what was ahead. He had pancreatic cancer metastatic to his liver. He responded well to FOLFIRINOX, but he hated it; the nausea, the vomiting, the diarrhea, the cold-induced neuropathy in Chicago in the winter. So he wanted to stop, but he was afraid because he saw what happened to his brother.

He enrolled in POLO. His treatment-related toxicity abated. He was able to lead a normal life. With each CT scan, his tumor got smaller and smaller, until 2 months ago, he was declared a complete response. And just last month, he spent his third Thanksgiving on POLO celebrating with his family.

Three years for metastatic pancreatic cancer to the liver; clearly, this is an outlier. But he's not the only patient to have prolonged disease control or prolonged response, and a prolonged time away from the toxicities of chemotherapy.

DR. HOFFMAN: Dr. Sanoff?

DR. SANOFF: I have to ask a question following on that. I think those stories are so incredibly meaningful. I will counter that by saying we have a patient in our practice who has germline BRCA-mutated pancreatic cancer, who has been on FOLFIRINOX and then continuous infusion on 5-FU leucovorin, and is now I think -- I can't remember because he's my partner's patient, but I think he's at 8 or 9 years from his systemic therapy for metastatic pancreatic cancer. We actually tried him off label on olaparib, and he couldn't tolerate it, and he kept trying, and he couldn't tolerate it.

So I think we really need to take a step back and look at these data. You guys showed the toxicity comparing olaparib to FOLFIRINOX, but as

Dr. Tempero mentioned, one of the options that people use is maintenance 5-FU leucovorin as a potential approach. We don't really know from the PANOPTIMOX trial what you might see from those results if you only use people who were progression-free from 6 months to out to -- what was it? You guys had somebody who had 41 cycles of FOLFIRINOX or something on that data.

So do you guys have a toxicity slide comparing 5-FU leucovorin to olaparib, to sort of show the group what that might look like?

DR. GALBRAITH: We don't have a slide doing that comparison. We do have a slide comparing with placebo that Dr. Patel showed. If you'd like to have a look at that slide from the core deck again, I'll invite Dr. Mayur Patel to describe those data.

DR. M. PATEL: Dr. Mayur Patel, AstraZeneca, patient safety. So what we don't have is the direct comparison that you've requested, but what we can share is that when you actually look in the maintenance setting of olaparib across the tumor

types in the pooled data set, what we do have are patients that have taken the olaparib for greater than 2 years, and that safety profile is actually no different in what we see in those patients who have taken it greater than 2 years versus what you see in the POLO trial.

So that gives us reassurance that the long-term safety profile actually looks good. Unlike in certain chemotherapeutic agents, we don't see cumulative toxicities, and we don't see patients requiring a drug holiday in that same because they're able to stay on therapy and that they're able to be maintained on the olaparib therapy through either interruptions and/or dose reductions, and the vast majority of our patients were able to tolerate the full dose in the POLO study.

DR. HOFFMAN: Dr. Hawkins?

DR. HAWKINS: Randy Hawkins, Charles Drew. I may have missed a slide, but I thought that on serious adverse side effects, there was a bowel perforation or [indiscernible]perforation. If

that's true, was that an outlier? The other question is, if the drug is approved, give me a feel for cost and availability of this drug in the treatment of the pancreatic cancer type we're talking about.

DR. GALBRAITH: To describe the case with the perforation, I'd like to invite Dr. Mayur Patel.

DR. HOFFMAN: I'm sorry. I'm going to interrupt. Although I understand, as a medical oncologist, the issues about cost and so on, I don't think that's within the purview of this discussion. Sorry.

DR. M. PATEL: Thank you very much. The patient that had the -- it was a duoedenal perforation. This patient was a female patient who had a history of bowel perforations that came into the study. May I see the slide on that report, please?

This patient came into the study with a history of bowel perforation. Six months after the initial bowel perforation that they had, they

entered into the study. They experienced a second bowel perforation that led to treatment discontinuation, and subsequently, after the 30-day follow-up period, the patient died. and it was reported as a grade 5 SAE.

So this patient, as I said, had a history of bowel perforation prior to entry into the study, entered 6 months after the first bowel perforation, and then subsequently died after the 30-day follow-up period due to progression of disease.

DR. HAWKINS: Thank you. Is the question of availability appropriate? Is the drug available? Will it be available?

DR. GALBRAITH: If the drug is approved and it will be made available, we will provide access programs for patients that have difficulties affording the medication.

DR. HAWKINS: That answers the question. Thank you.

DR. HOFFMAN: Dr. Reidy?

DR. REIDY: Yes. Can you comment on the 11 and a half response rate in the placebo arm? I'm

sure you looked at that a couple times.

DR. GALBRAITH: As Dr. Goessl described in his presentation, we do think that some of the responses that are seen in the placebo arm are due to carry-over effects of the platinum chemotherapy. You can see that on this slide from the core presentation, the onset of response in placebo was faster than that observed with olaparib and the durability also much shorter. We do have the details of those patients if you'd like more details.

DR. HOFFMAN: Dr. Hinrichs?

DR. HINRICHS: I'm sure this will come up in the discussion later, but I wanted to give the applicant a chance to comment on it. I think it's kind of the elephant in the room that in oncology, in metastatic solid tumors, and in pancreatic cancer specifically, we have a problem with the development and approval of expensive toxic agents with marginal efficacy, even agents that need a predefined endpoint; yet, we all realize that the actual benefit is marginal.

I'd like to ask the applicant to comment on how, with this application, they're taking us in a new and better direction in metastatic pancreatic cancer.

DR. GALBRAITH: The POLO study was conducted in an uncommon subset. Olaparib is a targeted therapy based on that the science underpins the sensitivity of the germline BRCA patient population to PARP inhibition. The benefit that we've seen here is not just confined to the primary endpoint with a 0.53 hazard ratio of improvement on that, but there's a totality of the data.

We have the improvement in the time to first subsequent therapy. We have the improvement at every landmark analysis on progression-free survival; highly durable response rates, including complete responses; and a well-tolerated safety profile with less than 5 percent of patients discontinuing therapy.

So the totality of all those data in this very difficult to treat disease is what we feel is support for full approval. It's also consistent

with what we've seen in terms of the activity of olaparib in multiple other germline BRCA-mutant patient populations, including ovarian cancer, breast cancer, and most recently described in prostate cancer.

DR. HOFFMAN: Are there any other questions for clarifying? Yes?

DR. KRAUS: Just one on response; that was the topic a minute ago. It's impressive to me the duration of response in 1 of 4 or 1 of 5 patients, and I didn't hear anything about assessment of those patients and whether there was any characteristic that might be specific and measurable and identifiable in that group. It often isn't so easy to do, I know; but I'm just wondering if you could comment on that subgroup because in this disease, that's particularly long, and it would be important to look at.

DR. GALBRAITH: I'd like to invite Dr. Gershon Locker to give some more details about the durable responders.

DR. LOCKER: Gershon Locker, global clinical

lead, AstraZeneca. We did look at the patients who had the long durable responses, and there was no characteristic which stood out. There were patients who initially had response to their chemotherapy; there were patients who had stable disease. There were patients predominantly Caucasian, but there was an African American patient who is among the long responders.

There were patients who had objective response who were long-term progression free, and there were some patients who only were stable on olaparib who had long-term, progression-free survival. There was no site specifically of metastasis. There were some in the usual liver and lung, but there were also patients who had metastasis in the peritoneum and in the pancreas primary.

So to answer your question, we cannot point out one group of patients who are more likely to do well long term than any other.

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

DR. SANOFF: Yes, just before you sit down, maybe. Are you looking at their tumor tissue and rolling that in? Because it is absolutely clear; some people did great on this, and it would be wonderful if we could select out the folks who have primary progression on a PARP inhibitor from the folks who have ongoing durable responses.

DR. GALBRAITH: Just in general, we are trying to understand, in greater detail, the predictive factors for both good response and resistance to olaparib across the clinical trial safety database. We did not collect tumor tissue at progression in the POLO study specifically, but that is a strong area of interest.

In terms of the patients that progressed quickly, we have done some analyses looking at characteristics that predicted for rapid progression, and I'd like to invite Dr. Nigel Baker to give those details.

DR. BAKER: Nigel Baker, biostatistician, AstraZeneca. Yes. We, like the FDA, noticed that the PFS curves went down pretty quickly, so we

wanted to understand what might be driving that particular feature; so what we did was to do a pretty intensive multivariate analysis. We included 15 different factors in a model, dividing patients into early progressors or later progressors, so logistic regression analysis. The only factor that was really driving that change was one of the quality-of-life measures, the patient's status assessment. Those with poorer patient status coming into the trial tended to be the ones who progressed earlier.

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

DR. HALABI: Yes, actually a follow-up to Dr. Hawkins' comments, and this is really a question for the agency.

If this is not approved, would the patients have access to the drug? That's one question. Then if it's not approved based on the data that we have presently in the application, let's say even though the conditional probability is very low in terms of overall survival ranging between 5 to 16

percent, would the sponsor have the opportunity to come back to the agency with the same application?

DR. PAZDUR: Yes, of course, they would have the opportunity to come back with new data or re-analysis of this data at any time. As in regard to availability, obviously this falls into off-label use of a approved drug.

DR. LEMERY: I think it's worth also saying, though, that based on this study, the conditional power for survival is low. It wasn't powered for survival effect to match the PFS effect. So if you're going to absolutely require OS, then they'd probably have to conduct another study.

Now, as an agency, we haven't always required OS, and we do have to recognize that this is a rare patient population that's hard to enroll, and if you had to, as AstraZeneca, I don't know what the actual numbers would be; if it would be 20,000 or 5,000, but it still is going to be a lot of patients. This was 4 years to enroll 150, so I think from a practicality standpoint, this is a challenging disease space to conduct studies in,

and we have to be cognizant of that.

DR. HOFFMAN: We'll now take a 12-minute break.

(Laughter.)

DR. HOFFMAN: I'll remind the panel members, please remember that there should be no discussion of the meeting topic during the break, amongst yourselves or with any members of the audience. We'll resume again at 10:30. Thank you.

(Whereupon, at 10:18 a.m., a recess was taken.)

Open Public Hearing

DR. HOFFMAN: 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's 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, speak only when recognized by the chairperson. I thank you for your cooperation.

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

MS. SCHLAGER: Thank you.

Good morning. My name is Lisa Schlager, and I'm pleased to speak on behalf of FORCE, the only national nonprofit devoted to people and families affected by hereditary cancers. We've been providing support, advocacy, education, and research to this community for over 20 years.

For disclosure, FORCE has received financial support from AstraZeneca for our annual conference and educational programs. The company also supports advertising of clinical trials enrolling patients with hereditary cancer. AstraZeneca does not have input into the content of any of our

programs and no sponsors or financial supporters have influenced these comments.

Pancreatic cancer is the third leading cause of cancer-related death in the U.S., and its incidence is on the rise. It's one of the few cancers for which survival has not improved substantially for 40 years. For all stages combined, over 90 percent of pancreatic cancer patients die within five years of diagnosis.

Few risk factors for developing pancreatic cancer have been identified, but BRCA mutation carriers are known to be at increased risk. People with BRCA mutations face some of the highest known cancer risks of any population. These cancers develop younger and the mutation often affects multiple family members who pass their inherited mutation onto future generations. This community faces a disproportionate cancer burden, however, the unique biology of BRCA-mutated cancer cells offers potential therapeutic advantages.

Adoption of therapies that target the cancers in mutation carriers just makes sense. In

fact, the new NCCN guidelines, as we've noted, stress that everyone diagnosed with pancreatic cancer should undergo germline testing. For the hereditary cancer mutation community and millions of people we represent, therapies targeting BRCA and other mutation-associated cancers offer hope.

We first learned about PARP inhibitors over a decade ago, and since that time, we've followed the research, educated our community, and facilitated clinical trial enrollment. We are very motivated to participate in research. Still, completion of PARP trials has taken a long time, and in the interim, many people who could not access these agents or did not meet clinical trial criteria have died.

While the POLO trial demonstrated a modest overall benefit to patients with 20 percent of those receiving olaparib experiencing partial or complete tumor shrinkage, the benefit was quite extraordinary for a subset of these patients, with some deriving years off of chemotherapy.

The overall response rate in olaparib was

about 23 percent versus 11 and a half percent with placebo, and two patients achieved complete response with olaparib. Median duration, as noted, was 7.4 months versus 3.7 months in the placebo arm. Although overall survival was unchanged, those who received olaparib benefited from twice as much time off of chemotherapeutic drugs. This is notable because quality of life tends to be much better for patients when they're not on chemotherapy.

Pancreatic cancers in people with germline BRCA mutations are more likely to respond to platinum-based chemo, but chemotherapy can have many side effects, some of which intensify over time. Maintenance therapy, as noted, provides these patients with a chemo-free interval.

David Dessert, a BRCA2 survivor diagnosed in 2011, shared his story. He said, "Pancreatic cancer is a disease that predominantly affects an older population that is unwilling or unable to tolerate the harsh treatments that are most effective. For those healthy enough to tolerate

them, neuropathy develops quickly, causing patients to drop the platinum component. A PARP inhibitor could alleviate all of this as an effective platinum replacement while reducing the toxicities and improving and increasing the quality of remaining life."

We'd like to note that David's father, an Air Force veteran with retiring rank of Lieutenant Colonel, died from his BRCA-related pancreatic cancer earlier this year. Again, these families are burdened heavily.

POLO gives us confirmation that PARP inhibitors are active in BRCA-related pancreatic cancer. Research should continue to determine how to optimize their use, but in the meantime, use as maintenance therapy is an important step forward. People fighting pancreatic cancer need every benefit they can get. Olaparib gives us more time without disease and more time where we might avoid chemotherapy, translating to months or years of improved quality of life.

FORCE strongly supports FDA approval of

olaparib for maintenance therapy for BRCA-mutated pancreatic cancer. We also want to note that PARPs are working for BRCA-related cancers regardless of location, and patients need access as well. We firmly believe that this therapy can better the lives of BRCA-mutated patients fighting these deadly diseases. Thank you.

DR. HOFFMAN: Thank you very much.

Will the second speaker please step to the podium and introduce yourself? Please state your name and the organization that you're representing for the record.

MS. FLESHMAN: Good morning. My name is Julie Fleshman. I'm the president and CEO of the Pancreatic Cancer Action Network, a national nonprofit organization that I've had the honor to lead for the last 20 years. My disclosure is that AstraZeneca is a member of PanCAN's Scientific and Medical Affairs Industry committee. PanCAN has not been involved in the development of Lynparza, and I was not paid to be here today.

As we've heard already this morning,

pancreatic cancer is the third leading cause of cancer death in the United States, and the 5-year survival rate for all types of pancreatic cancer is just 9 percent. This is unacceptable. There is a desperate need for new and better treatment options.

Through PanCAN's patient services, we speak with more pancreatic cancer patients and caregivers than any other organization or institution in the world. Last year, we had over 14,000 new contacts to our program and over 41,000 interactions. We know that patients want treatment options. They want to understand how to best determine the best treatment option for them. They're excited about innovative trial designs, they're frustrated by clinical trial barriers, and they want to survive.

In 2014, PanCAN launched our Know Your Tumor personalized medicine service. Our goal was to better understand if a pancreatic cancer patient's molecular profile could impact treatment options for the patient. Last year, we published the results from the first 640 patients to receive Know

Your Tumor reports.

Twenty-seven percent of these patients had actionable alterations. A BRCA mutation would be considered an actionable alteration. Of the 27 percent of patients with an actionable alteration that went on a matched therapy, we saw a significant progression-free survival advantage. Today, as more data has been analyzed, we're also observing an increase in overall survival. These results have been presented at major conferences, and we're waiting their publication soon.

We understand how important the distinction is between progression-free and overall survival, but we also appreciate that for individuals facing a rapidly deadly disease like pancreatic cancer with limited treatment options, improved survival of any sort is meaningful for them and their families.

One of the notable populations that we and others have seen among pancreatic cancer patients are those with DNA damage repair alterations, including BRCA mutations. We recently published

data suggesting patients with metastatic pancreatic cancer who had germline or somatic BRCA mutations, or similar alterations, had the same overall survival as those without DNA damage repair alterations when treated with certain standard chemotherapies, but they live an average of 11 months longer when treated with platinum containing chemotherapy.

Although this data was collected in a real-world setting instead of a clinical trial, it supports the finding and other tumor types that BRCA-defective pancreatic cancer is also sensitive to agents that take advantage of the impaired ability to repair DNA damage. Now we're looking at maintenance therapy for these very same patients, those with germline BRCA mutations who responded to platinum chemotherapy.

As a pancreatic cancer patient advocate working in this field for 20 years, I find the idea of maintenance therapy absolutely thrilling and a remarkable step forward for patients and their families. Particularly notable is the most recent

NCCN guidelines that were published just recently on November 26, 2019. Lynparza is now included in a list of maintenance therapy options for good performance patients with germline BRCA mutations rather than it just being listed in a footnote to consider the drug. This indicates that experts believe there is compelling evidence in the value of Lynparza in this setting.

Today, we know that pancreatic cancer is extremely heterogeneous, and the treatment approaches must align with the varying nature of each patient's biology. This means that pancreatic cancer clinical trial designs must be sophisticated. The POLO trial is an excellent example, introducing a targeted therapy to maintain the positive response patients with germline BRCA mutations experience from platinum-containing chemotherapy.

It's our responsibility to pancreatic cancer patients to continue to push forward new better treatment options that utilize our understanding of the tumor biology and each

patient's unique attributes. We also want to ensure that patients have access to these treatments and they are covered by insurance. Approving a new treatment for patients with metastatic pancreatic cancer who are germline BRCA mutation is an exciting and important step forward as the field continues to march forward. Thank you for taking all of this into consideration as you review Lynparza today.

DR. HOFFMAN: Thank you.

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

MS. PERLIS: Good morning. My name is Allison Perlis, and I am a 39-year-old pancreatic cancer survivor from Potomac, Maryland. I would like to thank ODAC for the opportunity to speak at this hearing.

I was 36 years old at the time of my diagnosis with three young children, ages 3, 6, and 8. As a busy mom who exercised regularly,

generally ate well, and had no other major risk factors for cancer, I could never imagine a doctor would tell me I had a mass on my pancreas. I went to the ER for a CT scan after an ultrasound was inconclusive for gallstones. As you can imagine, things moved very quickly.

At the time, I was a candidate for surgery, so I began chemotherapy with gem-abraxane at Johns Hopkins weeks later. As I began this treatment, a family friend, Dr. Michael Hall from Fox Chase Cancer Center, encouraged me to pursue genetic testing given my age and the lack of any other big risk factors. As a result of this genetic testing, I found out that I had the BRCA2 mutation. If I was otherwise healthy, this would have been upsetting, but with pancreatic cancer, it was the key to life-saving treatment.

After two months on gem-abraxane, my next CT scan revealed the cancer metastasized on to my liver, and I was now considered stage 4 and inoperable. With the knowledge that I have the BRCA2 mutation, my oncologist, Dr. Daniel Laheru,

changed my chemotherapy regimen to FOLFIRINOX, and I was responsive. FOLFIRINOX began to shrink the lesions on my liver. After many months and cycles, it also wore me down. I would lie in bed for days during part of my infusion and after, and I had little energy between treatments. I could barely care for myself, let alone my children or be a wife.

By December of 2017, it was time for a chemo break, and I was desperate to take my children to Disney World. We made the decision, in partnership with my oncologist, that I would try Lynparza off label during the break from FOLFIRINOX. I considered clinical trials, but the risk was too great for my family. My quality of life dramatically improved once I began taking Lynparza. I could just take the pills at home without going to the hospital and without being hooked up to an IV for days at a time. The side effects of Lynparza were also much more manageable than FOLFIRINOX.

My next scan in early 2018 showed the

lesions on my liver were effectively gone as a result of the Lynparza. I responded so well that Dr. Christopher Wolfgang was able to take me to the OR for a Whipple in April of 2018. Following surgery, my medical team agreed I could try just being on Lynparza and not go back on FOLFIRINOX. I completed several months.

After a short break from chemotherapy, there was a spot identified on my liver again during a CT scan in December of 2018. We made a very out-of-the-box decision, and I went back on Lynparza. In February 2019, I was able to be the maid of honor at my best friend's wedding out of state. Lynparza allowed me this flexibility while it helped me fight cancer and continue to really live a life. I attended my youngest son's graduation from preschool and made lifelong memories with my family during a summer vacation.

Several months later, following no new growth, I was able to go back to the OR with Dr. Wolfgang, and he did a liver resection in July of 2019. I have not been on any chemotherapy

since, and my CT scan was clear as of last week. The negative, however, was the financial burden of taking this drug, and that burden was enormous.

Despite my positive reaction and my positive early clinical trials, my insurance company refused to pay any of the monthly cost of the medication because it was not approved for the treatment of pancreatic cancer. This immense monthly expense impacted my marriage deeply, and the added stress of having to petition my insurance company for coverage was frustrating and demoralizing. I received EOB after EOB explaining why my request was rejected.

None of this would be a concern if Lynparza was approved for this patient population. It very clearly has the ability to save lives for pancreatic cancer patients and change a terminal prognosis into a potentially curable illness. Today, however, only patients who can somehow pull together the massive amount of money required to cover the medication can afford this life-saving treatment. I have no doubt I would not be here

today without Lynparza. My children now talk about how mommy crushed cancer and look forward to raising money for PanCAN at PurpleStride.

Lynparza saved my life, and with broader availability via explicit approval for its use in pancreatic cancer patients, I know it can save many, many more lives and help families like mine. I absolutely feel it should be approved for this patient population as soon as possible. Patients need it today. Thank you.

DR. HOFFMAN: Thank you.

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

MS. ZELDES: Thank you for the opportunity to speak here today. My name is Nina Zeldes, and I'm here as a senior fellow speaking on behalf of the National Center for Health Research. Our center analyzes scientific and medical data and provides objective health information to patients, providers, and policymakers. We do not accept

funding from drug and medical device companies, so I have no conflicts of interest.

Pancreatic cancer is often deadly, and new treatment options are desperately needed. However, it's equally important that new treatments have been proven to be safe and effective and have a clear benefit for patients that outweigh the risks. It is not clear that this drug fulfills those goals.

First of all, we agree with the FDA scientists' assessment of the limitations of the study. Problems with the study include a small number of patients; the possibility that the patients in the experimental group differ from the other group; the use of a primary endpoint that doesn't reflect clinical benefit; and uncertainty measuring tumor size. These limitations make the evaluation of the risks and benefits associated with this drug difficult, if not impossible.

Next, it is not clear whether the chosen primary endpoint of progression-free survival is clinically meaningful for patients, particularly

since the study demonstrated only a small improvement, and, unfortunately, there is no evidence for increased survival; the study's secondary endpoint. At the same time, patients in the study experienced more adverse events, including fatigue, nausea, and constipation. These results indicate that the drug does not give patients more time or improve their quality of life. In fact, the adverse events will inevitably lower patient's quality of life.

Given the risks and the unproven clinical benefit, there is no urgency to approve this drug, especially since there are other treatments available. If this drug were to be approved, it is likely that some patients would choose this drug over the current treatment recommendations, not realizing that the current treatments have evidence of improved survival, but this new drug does not.

Patients and doctors often assume that when the FDA approves a cancer drug, it increases overall survival. That would be logical. When there are treatments that are proven to have

benefits that outweigh the risks, there is no need for the FDA to rush to approve a treatment that lacks that evidence.

As advisors to the FDA, it is essential that you speak on behalf of patient safety as you carefully consider the data available for how this drug could help or harm patients. Thank you for your careful scrutiny of the evidence.

Questions to the Committee and Discussion

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. The committee will turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

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

The question before the committee, is the risk-benefit assessment for olaparib as a maintenance therapy in patients with a germline BRCA mutation pancreatic cancer favorable? I will recommend that when we're discussing as a committee, that the members not state their vote in the process of their comments, but to discuss aspects of their thinking about it; and later when we vote, we will be asked to explain why we voted the way we did.

DR. HOTAKI: Does anyone have any comments for discussion? Kind of do the same thing with the questions; so just write your names down and if you want to bring up points for discussion about the question, in general. Just again, don't state how you're going to vote.

(No response.)

DR. HOTAKI: No discussion?

DR. HOFFMAN: Dr. Reidy?

DR. REIDY: Okay, I'm going to start. As an oncologist that takes care of pancreatic cancer, I want to first state to say that we all recognize

this devastating disease. Everything we do in medicine, particularly in oncology, is to help our patients and their family members, help them live longer and better lives. So the billion dollar question here today is does this drug help us achieve those goals? In medicine, we say first do no harm.

So when I look at data, there's no overall survival benefit. However, the big issue is the duration of response on those that do achieve benefit with a 24-month benefit, which is really unprecedented in this disease. So I do applaud the sponsors and the investigators for taking this devastating disease and defining it by the sophisticated trial, as our public hearing speaker are defined.

They did that in two ways. They did their first by ensuring that patients that did not respond to platinum-based therapies were not included, and then you needed, again, to have this germline mutation. So although the overall survival benefit did not improve based on this

drug, that was 18 months overall. But again, those that responded had a duration of response of 2 years, which exceeded that overall survival.

We have not, unfortunately, defined that subsegment of the population, which is very unsettling because I do think there are many patients that received this drug that, unfortunately, did not derive benefit and potentially did have harm. So I think I just wanted to make that clear, that the toxicities as noted by the health-reported outcomes are actually not trivial.

DR. HOFFMAN: Dr. Cristofanilli?

DR. CRISTOFANILLI: I wonder if there is an expectation to get a second-line overall survival benefit in a population that is extremely small. We just mentioned that the design should have been eventually of thousands of patients with a much longer time to wait for these patients. As you know, during this series, maybe the control group can change. Is placebo acceptable now? It seems like for these patients it was because it is a

sensitive group, but it may not be in the future because the knowledge keeps improving.

This is a targeted therapy, it's a personalized treatment, and I think it is probably reasonable to consider the progression-free survival over the response and limited toxicities. There is nothing different for what we know for this drug. Is overall acceptable?

DR. HOFFMAN: Yes? Dr. Kulke?

DR. KULKE: Sure. Matt Kulke from Boston University. In thinking about it, there are several components I think to consider. There were questions raised about the robustness of the PFS analysis, and at least in my interpretation, those results are pretty strong. I'm less concerned about some of the radiology questions.

It also seems to me that given this is such a small subset of patients, despite the fact that the standard for pancreatic cancer has been overall survival, I'm not sure it's reasonable or even feasible to really expect that we're ever going see survival data. That may remain an unanswered

question.

The real question, and the tougher question, at least in my mind, is PFS survival really meaningful for patients in comparison to the alternate? Which would be a shorter treatment break, and then going on IV chemo. At least that's what I'm struggling with right now.

DR. HOFFMAN: Dr. Aldridge?

DR. ALDRIDGE: Dawn Aldridge, Solutions Cancer Resource Center. As one who represents the patient community, I find that this study showed that the quality of life was good in both arms. This is exciting to have targeted therapy for metastatic pancreatic cancer to treat the patients with or without family history.

The response was good in terms of the quality of life, the progression, and the duration over 24 months. I think that because of the limited therapies that we have right now, I feel that this would in some way be favorable in terms of the treatment and being able to have that as well.

DR. HOFFMAN: Dr. Halabi?

DR. HALABI: I would like to first start by commending the sponsor for undertaking this trial in a group of patients with rare disease. As a statistician, I look at the study and I recognize that there are flaws. Obviously, there are no clinical trials without any flaws, the biggest one being the randomization with a 3 to 2 allocation ratio and also the small sample size.

As my other colleagues have alluded to, the tough question here is whether to use PFS as an indicator for tangible benefit to these patients. While I do recognize this will be, if this drug is approved, the first time that the FDA will have an approval based on PFS endpoint, I recognize that it's really not feasible to undertake another study in this setting. And considering that this is targeted therapy, and collectively in the oncology community, we have experience with this drug, this is something else to consider when we look at the risk-benefit ratio. Thank you.

DR. HOFFMAN: Dr. Sung?

DR. SUNG: Normally, when I think about the importance of PFS, I think about it in relation to overall survival, or the potential for a cure, or plateau in those survival curves. One of the things that just struck me about this is that you have a separation of the PFS curves around 3 to 6 months, very early, but you really don't see that separation in the overall survival curves.

Now, the sponsor did mention that additional overall survival data will be available at the end of 2020, so I think that's something that's interesting to take into account, but, unfortunately, that overall survival data is not available now.

The other thing I want to point out is that a number of people -- the sponsors, some members of the public -- have made a comment about the importance of the fact that patients are able to stop chemotherapy, but they are still on therapy. I have a lot of patients with maintenance therapy, and they struggle with maintenance therapy.

In contrast, patients on placebo, those are

the ones who truly are therapy free, and I have a lot of patients who are therapy free, where we're just giving them a true holiday, and they experience a number of benefits with that. I think it's hard to compare those two populations in this setting with the data that we have been presented.

DR. HOFFMAN: Dr. Hinrichs?

DR. HINRICHS: I'm struck, first of all, that it's an amazing trial. It's a difficult trial to conduct in the targeted settings where you have a high screen fail rate. I'm also struck by how this seems to be, in large part, the future of medicine, that we're increasingly going to be trying to develop highly effective treatments for smaller and smaller slices of the population, and that presents challenges in how we study drugs, and how we decide if they're effective, and whether to approve them.

One major challenge in this trial has been testing whether there is a overall survival benefit or a clear clinical benefit to the treatment. The data that we have are that there is an improvement

in progression-free survival, from 7.4 months to 3.8 months, which is an absolute increase of 3.6 months in PFS. Is that clear evidence of efficacy? The other data that we have, just in terms of assessing how active the drug is and how effective it might be, are the response rate, which was 10 percent in the placebo arm and 20 percent in the drug arm.

So this combined with the difference in PFS suggests to me that the drug does have some level of activity, but does it have clinical benefit? That is the question that I think we have to ponder.

Related to that, if it does have clinical benefit, why is it so difficult to study? Granted, it's hard to enroll patients and conduct a large trial, but when you have a highly active agent, efficacy can be demonstrated in a relatively small number of patients. In fact, drugs have been approved in single-arm trials, showing high response rates for a drug in a difficult disease.

So I think those are the factors that I'm

taking into consideration as I think about this.

DR. HOFFMAN: Dr. Uldrick?

DR. ULDRICK: Sure. I agree with the comments that were just made, and in particular the strong biologic rationale for this agent that demonstrated activity. So for me, really, the question is, is maintenance the right approach to using this agent in patients with metastatic pancreatic cancer?

In the absence of an overall survival benefit, I really would like to see a benefit in quality of life. Unfortunately, the way the study was conducted, I'm left wondering whether there is an improvement in quality of life for the participants who received maintenance olaparib.

DR. HOFFMAN: I had a comment myself, and Dr. Tempero alluded to this. If the standard of care had been to have therapy for X number of months and then to take a treatment break, although I certainly can see the value to the patient of having a treatment break in terms of side effects and so on, but not every patient is positive about

that idea. I mean, there's this sense of when is the blade going to come down again, so every scan is going to be fraught whether you're on treatment or not.

But the lack of treatment is very distressing to some patients because people know what the usual outcome is for pancreatic cancer, so it's sort of just waiting for that to happen. There might be some positive value, which I realize is not something that can be tested with data, but there may be some positive value to doing something as opposed to nothing. I'm just thinking as a patient might think.

Dr. Kraus?

DR. KRAUS: Thank you. Agreeing with a lot of the points you made, but it is unfortunate there wasn't a large survival advantage like we all would have loved to see. I would note in considering, though, it looked like while the PARP crossover was small, there was also imbalance in post-progression platinum therapy favoring the placebo group that may have impacted things.

I do think, given it's a targeted therapy and we struggle with this in this industry in general, as does FDA and others, the capability to do large trials to really get at small subgroups is a big problem, so survival is unlikely later to show a lot, in my personal opinion, just because of these crossovers and subsequent therapies.

I do think the PFS looked robust to me, supporting the comments about good imaging and good sensitivity work to try to look at it and see if it's robust. Personally, I do think I look strongly at the tail there, too, and the responders, which are probably driving the tail. To me, in this disease particularly, it's not just 2 years; there's a median of 2 years, and half the patients have longer than that, and to see that level of response is meaningful.

It's unfortunate they can't be better identified at this time, but that alone is meaningful. On the benefit-risk, I think the non-responders are likely the ones dropping off quicker, so the time frame with which toxicity is

observed and realized by the patient is a little different.

So those are some of the factors on benefit itself. I think the toxicity of alternatives, that is, the next treatment, is very significant in most effective next treatments to be considered, which has been noted and the delay of symptomatology of the tumors.

To me, a point that's not been brought up -- perhaps the patient advocates did it most strongly -- was having a personal relationship with somebody who did have pancreatic cancer and the family situations and others around cancers. Being a patient and not being in a progressive disease situation is probably meaningful, even if they're not responding. So delaying progression, particularly in a dire disease, perhaps has that kind of a patient implication that's hard to dissect out of the data, and those of you who treat the disease probably know it far better than I.

DR. HOFFMAN: Dr. Pazdur? Dr. Sanoff?

DR. SANOFF: I echo a lot of those comments.

I think my biggest struggle here in trying to understand this is not the relevance of a PFS because I think that's pretty robust. I agree that radiographic interpretation is totally doable in pancreatic cancer. I don't have any concerns about that. I also think it's adamantly clear that this drug works in this disease. There are some people who get a ton of benefit.

The thing that I have struggled with since I first saw these results presented is where does this drug fit in the pancreatic cancer armamentarium? With my retrospectoscope, I would have, if I could, waved a magic wand and design this trial very differently.

I think, actually, absolutely as Dr. Hinrichs was saying, you can conduct a study that shows overall survival benefit where you have a very active disease in a small subset of the population. For instance, had this been designed as a second- or third-line trial, we would maybe be having a very different discussion rather than a maintenance approach.

Now, does that give patients the same clinical benefit in terms of time off therapy? I don't know, but I am a little concerned that overall survival curves don't separate at all, which means that we are probably really only benefiting a very small subset. On the flip side, you want that small subset to get this really effective drug. We just heard such a passionate plea for why that's important.

So I think that this is very difficult because you have an active drug, but a study that doesn't really help us know what the best way to use this drug is.

DR. HOFFMAN: Dr. Pazdur?

DR. PAZDUR: The reason why we brought this is really to demonstrate the problems that you've discussed here.

(Laughter.)

DR. PAZDUR: If this was garden variety adenocarcinoma, we'd definitely demand overall survival and end of the story, so to speak. But this really demonstrates the difficulty in

developing drugs that are targeted in a niche population, where you have a very small number of patients and where sometimes just saying, well, overall survival is the gold standard and we're not going to take a look at anything else, is probably to the detriment of patients. We really want to address this in a public hearing that we're looking at alternative endpoints here.

I think it's important, even when we discuss the magnitude of difference in progression-free survival, that we have to put it in the context of the disease and not take a look simply at the median. As Al pointed out, the hazard ratio was 0.5, which represents a 50 percent decrease in progression or death, so to speak. The reason why the medians are so small, you're taking a look at a rapidly progressive disease. If we had that same hazard ratio of 0.5 in CLL, we'd be talking about years here against the placebo.

So you have to put it in the context of the disease, really, to be fair about what we are doing here. But I think, really, what this represents is

where we have to go as we evaluate drugs. For some of the targeted therapies in other diseases, we have given full approval on the basis even of a single-arm trial with very high response rates.

We can't take a look at overall survival. Why? You simply don't have the numbers of patients there. Other reasons, sometimes you don't have equipoise. You know what the response rate is in a disease for a specific drug, and you simply can't randomize it against a placebo or a drug that has a relatively ineffective therapy associated with it; or a small response rate; or the disease, not like this, but, for example, in CLL; or even now in multiple myeloma where you have long natural histories of the disease because of either recent therapeutic interventions or just due to the natural history of the disease in itself. So there has to be some degree of flexibility here in looking at these therapies.

I think as we move on in the development of this drug -- and here again, I'd like some discussion because here again, there was an attempt

to do a randomized study, but if one went to more of a tissue agnostic type of indication for this type of therapy, we're probably going to have to be taking a look at single-arm studies and response rates in refractory diseases because it's simply going to be impossible even to take a look at progression-free survival when you just have a handful of patients.

So here again, we really congratulate the committee on their discussions. It's the same discussions that we had internally, but we wanted to get this out in a public forum. We've had our critics who say the FDA is lowering standards here because we are not demanding two trials, randomized, showing a survival advantage, but people have to be realistic. Simply, it can't be done in all situations.

I think, as I stated before, when we wrote this guidance on adenocarcinomas, we were looking at a fairly common disease here, adenocarcinoma with very few treatment options, so you could do survival studies. In this subset of patients,

obviously with this BRCA mutation, it's going to be very difficult to demand a survival advantage, but thank you for agreeing with all of our comments that we've had here internally.

DR. HOFFMAN: If there is no further discussion on this question, let's begin the voting process. 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 have 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 will go around room, and each individual who voted will state their name and vote into the record, and you can also state the reason why you voted as you did if you want to.

So any questions about that process?

(No response.)

DR. HOFFMAN: 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 it, please press the corresponding button again before the vote is closed.

(Voting.)

DR. HOTAKI: For the record, the vote is 7 yes, 5 no, zero abstentions.

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

DR. KULKE: Matt Kulke at Boston University. I voted yes. I think the evidence does show that this drug has activity in advanced pancreatic cancer. What I really thought about is, if you

think about this from a patient standpoint, would you want the option of being at home, for on average 7.4 months, on an oral agent or taking a short treatment break, and then going right back to the clinic and getting IV chemo.

I think having treated many patients, that many patients would opt for the option of an oral drug and being able to stay at home longer, and I think that's a benefit.

DR. HOFFMAN: Dr. Reidy?

DR. REIDY: Diane Reidy. I also voted yes. I would just echo what Matt said, and I want the public speaker that spoke on behalf of public policy to also recognize that this was a challenge because I don't want our patients to be harmed by drug, and we absolutely don't want our patients to refrain from platinum-based therapy.

That's a home run in this treatment. This drug is not a home run for the vast majority of patients, but I do think it was done in a way that we could enrich your patient population that will derive benefit, and I think that they deserve to

have that opportunity to have the drug.

DR. HOFFMAN: Dr. Aldridge?

DR. ALDRIDGE: Dawn Aldridge. I voted yes. I believe that this is something that would be beneficial for our patients to at least have the opportunity or at least the alternative to try.

DR. HOFFMAN: Dr. Hawkins?

DR. HAWKINS: Randy Hawkins, Charles Drew. I voted yes. I believe this is an opportunity for improved understanding of this rare cancer and to get a better understanding of how targeted therapy can work in this setting. I believe in what was said before, but I think that, really, with wide use, we'll understand more about the cancer and how this drug can impact it.

DR. HOFFMAN: Dr. Sung?

DR. SUNG: Anthony Sung. I voted no. While I agree with Dr. Kulke that I could see some patients preferring to spend 7 months on an oral drug at home versus 3 months off with no therapy, the sponsors did not present data supporting that. I think if they did present additional

health-related, quality-of-life data supporting that, I would have changed my vote to yes.

As I stated, I do believe PFS is an important endpoint, but I think it needs to be supported either by a difference in overall survival; or at least a trend towards a difference in overall survival; or some sort of hint in that direction; or additional evidence like healthcare-related quality of life.

Now, I do think that given a year or two with additional data, could I see myself changing my vote? Sure. But at this time, with the data I have in front of me, I do not think that data is sufficient. And again, I want to draw attention to the population of older adults, which, as stated earlier, I have some reservations about as well.

DR. HOFFMAN: Dr. Uldrick?

DR. ULDRICK: Thomas Uldrick. I voted no. I agree with basically the comments that Dr. Sung just stated. I really would have liked to see some evidence of quality of life and a study design that showed how to best use olaparib for pancreatic

cancer disease for which certainly a subset of patients benefit.

DR. HOFFMAN: Dr. Cristofanilli?

DR. CRISTOFANILLI: Massimo Cristofanilli. I voted yes. I think that the clinical data are supportive of efficacy for this drug. I think this approach is innovative, meaning giving the opportunity to patients that are candidates to access the drug on label and not off label. At the same time, I think that, over time, maybe the real-world data will show that there is a survival advantage.

DR. HOFFMAN: I'm Philip Hoffman. I voted yes. I will say that when I came in here this morning, I was very much on the fence, leaning toward no, largely because of the lack of overall survival data. But I voted yes because I think that although this is a subset of a subset who has the very prolonged benefit, the subset that BRCA carries, which is a small group, and then a group of those who have the prolonged benefit, I'm impressed by that benefit and would hate to think

that that benefit would not be available to those patients.

That's what Dr. Pazdur I think was referring to with respect to targeted therapies and the potentially very limited populations to whom they may apply.

Dr. Halabi?

DR. HALABI: Susan Halabi. I voted no, and I was on the fence. Again, I would have preferred a non-binary vote, maybe something fluid on the Likert, say from 1 to 10 --

(Laughter.)

DR. HALABI: -- but that would be more difficult for the FDA to analyze.

(Laughter.)

DR. HALABI: I have no issues with PFS as a measure of tangible benefit to the patients, and I do recognize that it's a very difficult trial to conduct, and it's not feasible to do a similar trial. However, the reason I voted no is because I want to see additional data. So if the sponsor will come back with additional data and we have

this opportunity, probably my answer would be yes. My vote will be yes. Thank you.

DR. HINRICHS: Christian Hinrichs. I voted no. The reason why is because when presented with the question of whether the risk-benefit ratio is favorable, I don't have enough data to conclude that it is. I say that on the basis of the data being a modest improvement in PFS, no improvement in quality of life, and a relatively low response rate at 10 percent in placebo and 20 in the treatment arm.

I reject the argument that an overall survival endpoint is impossible. It's impossible only if the agent is marginally active. For a highly active agent, overall survival would be a feasible endpoint. I would also say that for a highly active agent, a single-arm trial simply showing responses in refractory patients would be an acceptable endpoint. That's the reason for my vote.

DR. KLEPIN: Heidi Klepin. I voted no. Similar to many of the no votes, I was on the fence

this morning and was hoping to be convinced otherwise, but I voted on the totality of the data presented. I think there is some uncertainty around the magnitude of the benefit of the primary outcome. So I would call that, as was reported, a modest benefit at best. When I think about my patients and as we discuss treatment decisions, we're generally talking about a treatment in the context of it's going to help you live longer or better, meaning better quality of life, typically, in some construct or hopefully both.

So I would like to see a modest benefit in an imaging-related outcome, which I think needs some additional clinical patient-oriented support to see either a survival advantage, which we've all discussed -- and I agree that if there were a big effect, we would see it -- or some effect that I could say your quality of life is going to be better. And it simply was not supported by the data presented, unfortunately.

DR. SANOFF: Hanna Sanoff. I voted yes, and I voted yes because I think, ultimately, the

question of does the risk-benefit ratio favor olaparib in advanced pancreatic cancer, the answer is heck yeah because pancreatic cancer's risk is ultimate. I think the small proportion of people who benefit are really the ones who sway me here, and it's actually very akin to what we've now become used to with immune checkpoint inhibitors, which we use all the time, where the vast majority of people, at least in gastrointestinal cancers, don't benefit. But sometimes they do, and they benefit a whole heck of a lot, and that's what we saw here.

So I think the germline BRCA-mutated folks deserve to have that same opportunity as we've been giving to a variety of people in many, many solid tumors with checkpoint inhibitors.

DR. HOFFMAN: Thank you for your votes and your comments. As we've said earlier, the vote here is 7 yes, 5 no, and no abstentions. To just summarize, the favorable aspects leading to yes votes were that there does appear to be activity of this drug. It definitely prolongs progression-free

survival. There doesn't seem to be much question about that, and that olaparib's toxicity is not major for most patients, certainly not life threatening. So from the standpoint of risk-benefit of taking the drug, there seems to be more benefit than detriment.

The no votes raise the concern about the lack of overall survival data, certainly at this point. The fact of the similarity of quality of life, there's not been demonstrated and improved quality of life with taking the drug, and people would like to have additional data to consider, and that this is a relatively modest amount of benefit.

I hope I've accurately capsulized it. I think we've been over the themes quite thoroughly this morning.

Are there any other comments from the FDA about this?

(Dr. Pazdur gestures no.)

Adjournment

DR. HOFFMAN: We'll now adjourn the morning session and break for lunch. We will reconvene in

this room at 1:00, at which time we'll begin the afternoon session. I thank everyone for their attention and consideration here.

(Whereupon, at 11:28 a.m., the morning session was adjourned.)