

1 FOOD AND DRUG ADMINISTRATION
2 CENTER FOR DRUG EVALUATION AND RESEARCH

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4
5 ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING
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8
9 Tuesday, December 17, 2019
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11 Morning Session
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13 8:00 a.m. to 11:28 a.m.
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17

18 FDA White Oak Campus
19 White Oak Conference Center
20 Building 31, The Great Room
21 10903 New Hampshire Avenue
22 Silver Spring, Maryland

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P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

1 DR. HOFFMAN: Good morning. I'd first like
2 to remind everyone to please silence your cell
3 phones, smartphones, and any other devices if
4 you've not already done so. I would also like to
5 identify the FDA press contact, Brittney
6 Manchester. If you're present, please stand.
7 Thank you.

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

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

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

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

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

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

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

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

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

13 DR. HOTAKI: Lauren Hotaki, designated
14 federal officer.

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

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

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

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

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

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

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

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

9 DR. HOFFMAN: For topics such as those being
10 discussed at today's meeting, there are often a
11 variety of opinions, some of which are quite
12 strongly held. Our goal is that today's meeting
13 will be a fair and open forum for discussion of
14 these issues and that individuals can express their
15 views without interruption. Thus, as a gentle
16 reminder, individuals will be allowed to speak into
17 the record only if recognized by the chairperson.
18 We look forward to a productive meeting.

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

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

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

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

13 DR. HOFFMAN: Oh, sorry.

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

16 **Conflict of Interest Statement**

17 DR. HOTAKI: The Food and Drug
18 Administration is convening today's meeting of the
19 Oncologic Drugs Advisory Committee under the
20 authority of the Federal Advisory Committee Act of
21 1972. With the exception of the industry
22 representative, all members and temporary voting

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

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

11 FDA has determined that members and
12 temporary voting members of this committee are in
13 compliance with federal ethics and conflict of
14 interest laws. Under 18 U.S.C. Section 208,
15 Congress has authorized FDA to grant waivers to
16 special government employees and regular federal
17 employees who have potential financial conflicts
18 when it is determined that the agency's need for a
19 special government employee's services outweighs
20 his or her potential financial conflict of
21 interest, or when the interest of a regular federal
22 employee is not so substantial as to be deemed

1 likely to affect the integrity of the service which
2 the government may expect from the employee.

3 Related to the discussion of today's
4 meeting, members and temporary voting members of
5 this committee have been screened for potential
6 financial conflicts of interest of their own, as
7 well as those imputed to them, including those of
8 their spouses or minor children and, for purposes
9 of 18 U.S.C. Section 208, their employers. These
10 interests may include investments; consulting;
11 expert witness testimony; contracts, grants,
12 CRADAs; teaching, speaking, writing; patent and
13 royalties; and primary employment.

14 During the morning session, the committee
15 will discuss supplemental new drug application
16 208558/010 for Lynparza, olaparib, tablets
17 submitted by AstraZeneca Pharmaceuticals LP. The
18 proposed indication, use, for this product is for
19 the maintenance treatment of adults with
20 deleterious or suspected deleterious gBRCAm
21 metastatic adenocarcinoma of the pancreas, whose
22 disease has not progressed on the first-line,

1 platinum-based chemotherapy.

2 This is a particular matters meeting during
3 which specific matters related to AstraZeneca's
4 supplemental NDA will be discussed. Based on the
5 agenda for today's meeting and all financial
6 interests reported by the committee members and
7 temporary voting members, no conflict of interest
8 waivers have been issued in connection with this
9 meeting.

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

22 To ensure transparency, we encourage all

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

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

16 **FDA Opening Remarks - Martha Donoghue**

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

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

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

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

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

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

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

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

5 The primary efficacy outcome measure for the
6 POLO trial was progression-free survival, or PFS,
7 according to blinded, independent central review
8 using the response evaluation criteria for solid
9 tumors, RECIST, version 1.1. The primary analysis
10 of POLO demonstrated a statistically significant
11 improvement in PFS in patients randomized to
12 receive olaparib compared to patients randomized to
13 placebo. The hazard ratio for PFS was 0.53 with a
14 95 percent confidence interval ranging from 0.35 to
15 0.81, corresponding to a median improvement in PFS
16 of 3.6 months.

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

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

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

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

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

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

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

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

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

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

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

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

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

4 The second issue relates to the limitations
5 of the POLO trial. This application is supported
6 by the results of a single randomized,
7 placebo-controlled trial. As noted earlier,
8 germline BRCA-mutated pancreatic cancer comprises a
9 small subgroup of patients with pancreatic cancer,
10 and the sample size of POLO is small at 154
11 patients. Additionally, although the trial had
12 80 percent power to show a 6-month improvement in
13 median overall survival, it was not adequately
14 powered to show a smaller improvement in overall
15 survival.

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

1 likelihood of demonstrating an improvement in
2 overall survival is low.

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

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

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

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

18 FDA is seeking the committee's opinion on
19 whether the risk-benefit relationship favors use of
20 olaparib for the proposed indication. This
21 concludes my remarks, and thank you for your
22 attention.

1 DR. HOFFMAN: Thank you.

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

9 For this reason, FDA encourages all
10 participants, including the sponsor's non-employee
11 presenters, to advise the committee of any
12 financial relationships that they may have with the
13 firm at issue such as consulting fees, travel
14 expenses, honoraria, and interest in the sponsor,
15 including equity interests and those based upon the
16 outcome of the meeting.

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

1 speaking.

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

4 **Applicant Presentation - Susan Galbraith**

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

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

22 Olaparib has a well-established safety

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

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

22 This selective mechanism of killing of

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

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

16 Tumor cells that are homozygous for BRCA
17 mutation are a thousand times more sensitive to
18 cell killing with a PARP inhibitor versus the wild
19 type or heterozygous BRCA-mutant cells. In
20 contrast, BRCA-mutant tumor cells are only about
21 10-fold more sensitive to cell killing with
22 platinum chemotherapy than wild type or

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

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

16 The IND for the POLO trial was submitted in
17 2014. In discussions with the FDA about the
18 reliability of assessment of progression-free
19 survival in patients whose sole measurable disease
20 is in the pancreas, we focused the patient
21 population on metastatic disease. We also removed
22 the planned interim analysis for PFS. We

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

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

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

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

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

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

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

1 Our presentation today will cover the
2 following information:

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

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

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

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

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

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

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

20 **Applicant Presentation - Hedy Kindler**

21 DR. KINDLER: Thank you, Dr. Galbraith.

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

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

8 Metastatic pancreatic cancer has a dismal
9 prognosis, with the worst survival of any solid
10 tumor. The 5-year survival rate of this disease is
11 only 3 percent. About 57,000 Americans will be
12 diagnosed with pancreatic cancer in 2019 and about
13 46,000 will die from it. As this figure
14 illustrates, in the next year, pancreatic cancer is
15 projected to become the second leading cause of
16 cancer death in the United States. These abysmal
17 statistics reflect the early distant spread of
18 pancreatic cancer and the inadequacy of our current
19 therapies.

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

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

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

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

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

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

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

22 In the pivotal FOLFIRINOX trial, although

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

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

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

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

8 This slide illustrates the typical journey
9 of a patient with gBRCA-mutant metastatic
10 pancreatic cancer. These patients typically start
11 with FOLFIRINOX. Some will have a planned stop
12 after 6 months or they will most only receive about
13 5 months of therapy because cumulative toxicity
14 limits how long they can stay on the regimen.

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

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

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

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

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

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

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

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

3 **Applicant Presentation - Carsten Goessl**

4 DR. GOESSL: Thank you, Dr. Kindler.

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

11 The results of the multicohort Study 42
12 trial provided the rationale for developing
13 olaparib as a maintenance therapy for germline
14 BRCA-mutated metastatic pancreatic cancer. Study
15 42 included 23 metastatic pancreatic cancer
16 patients with germline BRCA mutations. They
17 received olaparib as a second-line or later
18 therapy. We observed an objective response rate
19 of 22 percent.

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

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

5 POLO is a well-conducted, randomized,
6 double-blind placebo-controlled trial in
7 adenocarcinoma of the pancreas in the maintenance
8 setting. We screened 3,315 patients taken over
9 4 years to randomize 154 patients with a gBRCA
10 mutation. In terms of screening, this is clearly
11 the largest prospective study in pancreatic cancer
12 ever undertaken.

13 Patients had received at least 16 weeks of
14 platinum-based chemotherapy with no upper limit to
15 ensure that patients have adequate platinum
16 exposure, and they must not have progressed on
17 chemotherapy. We randomized 154 patients in a 3 to
18 2 fashion. Thus, 92 patients were randomized to
19 olaparib 300-milligram tablets twice daily and 62
20 patients to placebo.

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

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

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

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

1 and there was adjustment protesting [indiscernible]
2 overall survival twice. An interim OS analysis was
3 to be conducted at the time of the final PFS
4 analysis. A final OS analysis will be done when
5 106 test events have occurred.

6 We required a minimum of 16 weeks of
7 first-line, platinum-based chemotherapy. Patients
8 who had a response or stable disease to platinum
9 chemotherapy, they're randomized within
10 4 to 6 weeks to either olaparib or placebo.
11 Patients continued blinded maintenance treatment
12 until disease progression. Afterwards, many
13 patients went on to receive multiple subsequent
14 lines of chemotherapy.

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

1 that all endpoints were measured from
2 randomization.

3 Fifty-nine percent of patients in the
4 olaparib arm discontinued due to disease
5 progression compared with 79 percent in the placebo
6 arm. Discontinuations for other reasons were
7 similar between arms. Notably, one sort of
8 patients in the olaparib arm was still continuing
9 on assigned study treatment at the data cutoff
10 compared with only 13 percent in the placebo arm.
11 We had a median follow-up for progression of
12 9 months in the olaparib arm and 4 months in the
13 placebo arm.

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

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

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

14 Median progression-free survival was 7.4
15 months in the olaparib arm. This is almost double
16 as the progression free survival in the placebo,
17 which was 3.8 months in line with expectations. Of
18 note, a substantial proportion of patients in the
19 olaparib arm remained free of progression beyond
20 2 years. This tail suggests that olaparib is
21 associated with a prolonged benefit.

22 Consistently, at every prespecified landmark

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

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

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

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

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

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

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

1 olaparib with a hazard ratio of 0.91, this did not
2 reach statistical significance. The median overall
3 survival was 18.9 months in the olaparib arm versus
4 18.1 months in placebo.

5 In a larger study, this hazard ratio might
6 translate to a 2-month improvement in median
7 overall survival. We will have a final overall
8 survival analysis at 106 events, which is expected
9 to occur late next year. The conditional power is
10 9 percent to detect an overall survival difference
11 at the final overall survival analysis.

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

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

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

17 Objective response rate was determined in
18 the 84 percent of patients who had measurable
19 disease at study entry. We observed a 23 percent
20 response rate in the olaparib arm, including
21 2 complete responses, compared with an 11.5 percent
22 response rate in the placebo arm, which is likely a

1 carryover effect from chemotherapy.

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

12 This analysis is not mature, the hazard
13 ratio is 4.76, and it is not statistically
14 significant. But you do see separation of the
15 curves in favor of olaparib, starting at about
16 8 months.

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

1 100 scale in both arms. Higher scores indicate
2 better health-related quality of life, and a
3 10-point change from baseline was predefined as
4 clinically meaningful.

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

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

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

1 statistically significant and clinically meaningful
2 47 percent reduction in the risk of disease
3 progression or death compared with placebo. POLO
4 also demonstrated a meaningful benefit to patients
5 in multiple key secondary endpoints.

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

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

22 In conclusion, the totality of the evidence

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

7 **Applicant Presentation - Mayur Patel**

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

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

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

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

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

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

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

1 exposure on the olaparib arm was approximately
2 1.6 times longer than in the placebo arm.

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

12 The relatively large number of
13 placebo-treated patients experiencing either a high
14 grade or a serious adverse event reflects a high
15 burden of disease in this patient population.
16 There were no treatment-emergent adverse events
17 with a fatal outcome in either arm. After the
18 30-day follow-up period, 2 patients in the olaparib
19 died from causes not considered to be due to
20 disease progression by the reporting investigator;
21 one from an unknown cause and the other due to
22 refractory septic shock while receiving cisplatin

1 and gemcitabine as a subsequent therapy.

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

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

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

1 intervention.

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

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

22 Only 5 patients discontinued olaparib due to

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

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

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

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

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

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

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

3 **Applicant Presentation - Margaret Tempero**

4 DR. TEMPERO: Thank you, Dr. Patel.

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

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

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

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

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

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

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

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

1 completely from the cumulative side effects of
2 chemotherapy.

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

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

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

20 **Applicant Presentation - Susan Galbraith**

21 DR. GALBRAITH: Thank you, Dr. Tempero.

22 You've heard from Dr. Kindler why germline

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

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

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

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

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

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

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

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

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

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

21 DR. HOFFMAN: Thank you very much.

22 We will now proceed with the presentation

1 from the FDA.

2 **FDA Presentation - Naomi Horiba**

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

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

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

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

22 The Kaplan-Meier curves for PFS are shown

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6 This slide shows the results of the analysis
7 for overall response rate, or ORR, in POLO. As a
8 reminder, ORR was assessed according to RECIST 1.1
9 and by blinded independent central review. As
10 shown, the overall response rate was approximately
11 20 percent in patients randomized to olaparib and
12 approximately 10 percent in patients randomized to
13 placebo.

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

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

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

14 In POLO, 60 patients in the olaparib arm and
15 44 in the placebo arm experienced disease
16 progression. Of these, approximately 60 percent
17 were determined to have progressed based on
18 findings in a single anatomic site. Overall,
19 approximately 20 percent of patients with disease
20 progression were diagnosed with progression based
21 solely on findings in the pancreas or peritoneum,
22 sites which are recognized to be difficult to

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

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

14 I will now discuss the limitations of the
15 POLO trial. The first limitation relates to the
16 small sample size of the POLO trial. As a
17 reminder, the efficacy population in POLO consists
18 of 154 patients. POLO was designed to have 80
19 percent power to detect a hazard ratio of 0.57 for
20 OS. Based on occurrence of 106 events, assuming a
21 median OS of 8 months in the placebo arm and
22 14 months in the olaparib arm, the prespecified

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

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

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

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

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

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

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

1 of olaparib on overall survival.

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

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

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

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

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

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

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

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

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

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

19 **Clarifying Questions to Presenters**

20 DR. HOFFMAN: Thank you very much.

21 We'll now take clarifying questions for the
22 presenters. Please remember to state your name for

1 the record before you speak, and if you can, please
2 direct your questions to a specific presenter.

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

8 DR. HOFFMAN: Please?

9 DR. SUNG: Anthony Sung, Duke university.
10 Would the sponsor please pull up, let's see here,
11 CE-13? Looking at the patients who are older than
12 65 years, which is about a third of the patients in
13 the study, there's not even a trend to a favorable
14 progression-free survival in this population.

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

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

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

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

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

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

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

5 Dr. Kindler? Dr. Locker, perhaps?

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

14 So we can see no difference here, and the
15 same goes for those patients who are now on for
16 3 years. The percent of patients who get long-term
17 benefit is no different in the older group of
18 patients than in the younger. So the issue is not
19 older patients; the issue is the overall results.
20 They do about the same and, again, the question is
21 whether in multiple subset analyses, you're not
22 likely to find one where it looks a little

1 different from all the others.

2 DR. HOFFMAN: Dr. Klepin?

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

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

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

13 Dr. Patel?

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

1 and discontinuations were largely similar between
2 the patient populations.

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

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

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

12 DR. HALABI: Thank you.

13 DR. HOFFMAN: Dr. Hawkins?

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

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

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

4 Dr. Patel?

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

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

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

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

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

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

1 quality of life, actually.

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

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

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

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

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

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

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

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

1 imbalance receiving platinum therapy on olaparib.

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

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

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

22 DR. GALBRAITH: We did look at the response

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

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

21 Can such a comparison be made?

22 DR. GALBRAITH: I'd like to invite

1 Dr. Nikunj Patel to provide further details. As
2 he's coming to the podium, we did collect quality
3 of life through to the time of progression and
4 30 days after, and Dr. Patel could show those data.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

13 DR. HALABI: Yes, absolutely. I do
14 recognize that. A follow-up to that, since, FDA,
15 you mentioned that you're still looking at the
16 data, is it legitimate to ask if there is updated
17 data? Because the cutoff point was earlier in
18 2019. So is it a legitimate question to ask the
19 sponsor to present updated data?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

13 Dr. Schwartz?

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

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

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

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

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

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

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

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

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

1 overrides the lack of precision in measuring. For
2 instance, in the pancreas, the overall magnitude of
3 measurement was about 1.5 centimeters to
4 5 centimeter growth when the progression actually
5 occurred, and I think that that's within the
6 precision.

7 If I may, I'd just like to show two imaging
8 examples. This was one of the pancreas primary
9 target lesions, in the tail, near the spleen of the
10 pancreas, at baseline, measuring roughly
11 3.6 centimeters, and then at week 32,
12 6 centimeters. I think while the measurements we
13 could maybe debate a millimeter or two, I think it
14 was relatively straightforward to call this type of
15 lesion. You also notice that this is a very good
16 quality contrast IV and oral enhanced scan.

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

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

6 DR. HOFFMAN: Dr. Reidy?

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

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

1 both arms, as was the rate of stable disease.

2 DR. HOFFMAN: Dr. Sanoff?

3 DR. SANOFF: I'd like to ask a question
4 about the clinical relevance of these results when
5 you take them in the context of placebo-controlled
6 trial here. You all showed the data on about a
7 5-month FOLFIRINOX treatment in first line in the
8 Conroy trial, but I'm very curious to know if you
9 have an understanding of what the standard of care
10 is in the United States.

11 I know the NCCN guidelines say that a
12 chemotherapy holiday is a reasonable thing to do.
13 I don't actually necessarily agree with that. I
14 think if you look at the Conroy trial, there was
15 progression in about half of the people before
16 6 months, so I think that the idea that 5 months
17 was the actual treatment course in that trial is a
18 little bit misleading.

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

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

5 DR. GALBRAITH: So just a couple of things
6 to note. In order to be enrolled into the POLO
7 study, patients had to have received a minimum of
8 16 weeks of platinum-based chemotherapy, but could
9 go and continue on either FOLFIRI or 5-FU
10 monotherapy, so that didn't exclude them from
11 inclusion. Twenty percent of the patients in the
12 POLO study were from the United States and Canada,
13 and representative of treatment in this country.

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

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

1 6 months of therapy, assuming the therapy's been
2 successful. In the U.S., it varies quite a bit,
3 from chemotherapy holiday, as we do at UCSF, versus
4 some ongoing form of chemotherapy, I think as Hedy
5 pointed out, and maybe dropping drugs over time.

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

18 DR. HOFFMAN: Dr. Klepin?

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

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

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

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

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

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

1 follow-up question?

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

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

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

22 Is there evidence to suggest that this is

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

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

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

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

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

3 DR. HOFFMAN: Dr. Cristofanilli?

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

12 The question would be, eventually, if you
13 can take a PARP inhibitor between two chemotherapy
14 treatments, would this improve survival?

15 Obviously, I think this is going to take a longer
16 time because you selected patients that are
17 sensitive. Do you have any sense or do you have
18 any data for the patients that do not achieve
19 response but were with stable disease when they
20 entered the study, if they had a superior benefit
21 or not?

22 DR. GALBRAITH: As Dr. Goessl showed in the

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

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

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

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

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

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

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

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

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

6 DR. HOFFMAN: Dr. Sanoff?

7 DR. SANOFF: I have to ask a question
8 following on that. I think those stories are so
9 incredibly meaningful. I will counter that by
10 saying we have a patient in our practice who has
11 germline BRCA-mutated pancreatic cancer, who has
12 been on FOLFIRINOX and then continuous infusion on
13 5-FU leucovorin, and is now I think -- I can't
14 remember because he's my partner's patient, but I
15 think he's at 8 or 9 years from his systemic
16 therapy for metastatic pancreatic cancer. We
17 actually tried him off label on olaparib, and he
18 couldn't tolerate it, and he kept trying, and he
19 couldn't tolerate it.

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

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

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

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

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

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

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

18 DR. HOFFMAN: Dr. Hawkins?

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

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

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

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

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

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

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

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

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

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

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

20 DR. HOFFMAN: Dr. Reidy?

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

1 sure you looked at that a couple times.

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

12 DR. HOFFMAN: Dr. Hinrichs?

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

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

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

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

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

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

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

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

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

22 DR. LOCKER: Gershon Locker, global clinical

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 Now, as an agency, we haven't always
15 required OS, and we do have to recognize that this
16 is a rare patient population that's hard to enroll,
17 and if you had to, as AstraZeneca, I don't know
18 what the actual numbers would be; if it would be
19 20,000 or 5,000, but it still is going to be a lot
20 of patients. This was 4 years to enroll 150, so I
21 think from a practicality standpoint, this is a
22 challenging disease space to conduct studies in,

1 and we have to be cognizant of that.

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

4 (Laughter.)

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

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

12 **Open Public Hearing**

13 DR. HOFFMAN: Both the Food and Drug
14 Administration and the public believe in a
15 transparent process for information gathering and
16 decision making. To ensure such transparency at
17 the open public hearing session of the advisory
18 committee meeting, FDA believes that it's important
19 to understand the context of an individual's
20 presentation.

21 For this reason, FDA encourages you, the
22 open public hearing speaker, at the beginning of

1 your written or oral statement to advise the
2 committee of any financial relationship that you
3 may have with the sponsor, its product, and if
4 known, it's direct competitors. For example, this
5 financial information may include the sponsor's
6 payment of your travel, lodging, or other expenses
7 in connection with your attendance at this meeting.

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

15 The FDA and this committee place great
16 importance in the open public hearing process. The
17 insights and comments provided can help the agency
18 and this committee in their consideration of the
19 issues before them. That said, in many instances
20 and for many topics, there will be a variety of
21 opinions.

22 One of our goals today is for this open

1 public hearing to be conducted in a fair and open
2 way, where every participant is listened to
3 carefully and treated with dignity, courtesy, and
4 respect. Therefore, speak only when recognized by
5 the chairperson. I thank you for your cooperation.

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

10 MS. SCHLAGER: Thank you.

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

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

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

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

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

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

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

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

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

22 The overall response rate in olaparib was

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

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

17 David Dessert, a BRCA2 survivor diagnosed in
18 2011, shared his story. He said, "Pancreatic
19 cancer is a disease that predominantly affects an
20 older population that is unwilling or unable to
21 tolerate the harsh treatments that are most
22 effective. For those healthy enough to tolerate

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

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

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

22 FORCE strongly supports FDA approval of

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

8 DR. HOFFMAN: Thank you very much.

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

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

22 As we've heard already this morning,

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

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

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

1 Your Tumor reports.

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

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

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

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

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

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

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

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

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

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

10 DR. HOFFMAN: Thank you.

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

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

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

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

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

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

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

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

22 My next scan in early 2018 showed the

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

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

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

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

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

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

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

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

11 DR. HOFFMAN: Thank you.

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

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

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

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

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

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

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

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

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

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

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

9 **Questions to the Committee and Discussion**

10 DR. HOFFMAN: Thank you.

11 The open public hearing portion of this
12 meeting is now concluded, and we will no longer
13 take comments from the audience. The committee
14 will turn its attention to address the task at
15 hand, the careful consideration of the data before
16 the committee, as well as the public comments.

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

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

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

17 (No response.)

18 DR. HOTAKI: No discussion?

19 DR. HOFFMAN: Dr. Reidy?

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

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

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

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

1 drug, that was 18 months overall. But again, those
2 that responded had a duration of response of
3 2 years, which exceeded that overall survival.

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

13 DR. HOFFMAN: Dr. Cristofanilli?

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

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

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

9 DR. HOFFMAN: Yes? Dr. Kulke?

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

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

1 question.

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

8 DR. HOFFMAN: Dr. Aldridge?

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

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

1 DR. HOFFMAN: Dr. Halabi?

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

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

22 DR. HOFFMAN: Dr. Sung?

1 DR. SUNG: Normally, when I think about the
2 importance of PFS, I think about it in relation to
3 overall survival, or the potential for a cure, or
4 plateau in those survival curves. One of the
5 things that just struck me about this is that you
6 have a separation of the PFS curves around 3 to
7 6 months, very early, but you really don't see that
8 separation in the overall survival curves.

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

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

22 In contrast, patients on placebo, those are

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

7 DR. HOFFMAN: Dr. Hinrichs?

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

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

1 in progression-free survival, from 7.4 months to
2 3.8 months, which is an absolute increase of 3.6
3 months in PFS. Is that clear evidence of efficacy?
4 The other data that we have, just in terms of
5 assessing how active the drug is and how effective
6 it might be, are the response rate, which was 10
7 percent in the placebo arm and 20 percent in the
8 drug arm.

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

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

22 So I think those are the factors that I'm

1 taking into consideration as I think about this.

2 DR. HOFFMAN: Dr. Uldrick?

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

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

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

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

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

14 Dr. Kraus?

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

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

8 I do think the PFS looked robust to me,
9 supporting the comments about good imaging and good
10 sensitivity work to try to look at it and see if
11 it's robust. Personally, I do think I look
12 strongly at the tail there, too, and the
13 responders, which are probably driving the tail.
14 To me, in this disease particularly, it's not just
15 2 years; there's a median of 2 years, and half the
16 patients have longer than that, and to see that
17 level of response is meaningful.

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

1 observed and realized by the patient is a little
2 different.

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

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

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

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

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

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

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

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

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

14 DR. HOFFMAN: Dr. Pazdur?

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

18 (Laughter.)

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

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

9 I think it's important, even when we discuss
10 the magnitude of difference in progression-free
11 survival, that we have to put it in the context of
12 the disease and not take a look simply at the
13 median. As Al pointed out, the hazard ratio was
14 0.5, which represents a 50 percent decrease in
15 progression or death, so to speak. The reason why
16 the medians are so small, you're taking a look at a
17 rapidly progressive disease. If we had that same
18 hazard ratio of 0.5 in CLL, we'd be talking about
19 years here against the placebo.

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

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

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

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

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

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

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

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

5 DR. HOFFMAN: If there is no further
6 discussion on this question, let's begin the voting
7 process. We'll be using an electronic voting
8 system for this meeting. Once we begin the vote,
9 the buttons will start flashing and will continue
10 to flash even after you have entered your vote.
11 Please press the button firmly that corresponds to
12 your vote. If you're unsure of your vote or you
13 wish to change your vote, you may press the
14 corresponding button until the vote is closed.

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

1 So any questions about that process?

2 (No response.)

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

11 (Voting.)

12 DR. HOTAKI: For the record, the vote is
13 7 yes, 5 no, zero abstentions.

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

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

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

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

10 DR. HOFFMAN: Dr. Reidy?

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

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

1 have that opportunity to have the drug.

2 DR. HOFFMAN: Dr. Aldridge?

3 DR. ALDRIDGE: Dawn Aldridge. I voted yes.

4 I believe that this is something that would be
5 beneficial for our patients to at least have the
6 opportunity or at least the alternative to try.

7 DR. HOFFMAN: Dr. Hawkins?

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

16 DR. HOFFMAN: Dr. Sung?

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

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

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

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

17 DR. HOFFMAN: Dr. Uldrick?

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

1 cancer disease for which certainly a subset of
2 patients benefit.

3 DR. HOFFMAN: Dr. Cristofanilli?

4 DR. CRISTOFANILLI: Massimo Cristofanilli.

5 I voted yes. I think that the clinical data are
6 supportive of efficacy for this drug. I think this
7 approach is innovative, meaning giving the
8 opportunity to patients that are candidates to
9 access the drug on label and not off label. At the
10 same time, I think that, over time, maybe the
11 real-world data will show that there is a survival
12 advantage.

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

1 that that benefit would not be available to those
2 patients.

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

7 Dr. Halabi?

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

12 (Laughter.)

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

15 (Laughter.)

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

1 this opportunity, probably my answer would be yes.

2 My vote will be yes. Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

17 Are there any other comments from the FDA
18 about this?

19 (Dr. Pazdur gestures no.)

20 **Adjournment**

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

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

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