FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC)

Morning Session

Wednesday, May 24, 2017

8:00 a.m. to 11:55 a.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31, The Great Room

Silver Spring, MD

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:11 a.m.)

Call to Order

Introduction of Committee

DR. RINI: Okay, Good morning everyone. We're going to go ahead and get started. I'd first like to remind everyone to silence your cell phones or other devices if you have not done so already. I'd also like to identify the FDA press contact, who's Angela Stark. Angela if you are present if you could please stand, she is in the back of the room.

We're going to go around now, and each panel member can introduce themselves, name, and where you're from and we'll start with Dr. Morrow down at the end.

DR. MORROW: Good morning. P.K. Morrow. I'm a medical oncologist. I'm with Amgen. I'm the industry rep.

DR. LIPKOWITZ: Stan Lipkowitz. I'm and oncologist and head of the Women's Malignancy Branch at NIH, NCI.

DR. MINASIAN: Lori Minasian, medical

oncologist, Division of Cancer Prevention at National Cancer Institute.

DR. NERENSTONE: Stacy Nerenstone. I'm a medical oncologist at Hartford Hospital.

DR. ROYCE: Melanie Royce. I'm a medical oncologist formally University of New Mexico, Albuquerque.

DR. SEIDMAN: Andrew Seidman, a medical oncologist for the Breast Medicine Service at Memorial Sloan Kettering.

MS. SPEARS: I'm Patty Spears, patient representative from Raleigh, North Carolina.

MS. PREUSSE: Courtney Preusse, consumer representative, program operations, Fred Hutch.

DR. ULDRICK: Thomas Uldrick, medical oncologist, Center for Cancer Research, NCI.

MR. COLE: Bernard Cole, biostatistics, University of Vermont.

DR. BURSTEIN: Hal Burstein, medical oncology, Dana-Farber Cancer Institute.

DR. RINI: I'm Brian Rini. I'm a GU medical oncologist from Cleveland Clinic.

DR. TESH: Lauren Tesh, designated federal officer for ODAC.

DR. NOWAKOWSKI: Greg Nowakowski, medical oncologist, Mayo Clinic, Rochester.

DR. RIELY: Greg Riely, medical oncologist, Memorial Sloan Kettering.

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

DR. PAPADIMITRAKOPOULOU: Vali Papadimitrakopoulou, medical oncologist, MD Anderson Cancer Center.

MR. D'AGOSTINO: Ralph D'Agostino, statistician at Boston University in the Framingham study.

MS. CHENG: Joyce Cheng, statistician, FDA.

DR. WALKER: Amanda Walker, clinical reviewer, FDA.

DR. SINGH: Harpreet Singh, clinical reviewer, FDA.

DR. AMIRI-KORDESTANI: Laleh Amiri, clinical team leader, FDA.

DR. BEAVER: Julia Beaver, acting director,

Division of Oncology Products I, FDA.

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

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

In the spirt of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that advisory committee members take care in their conversations about the topic at hand and that they take place in an open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or during lunch. Thank you.

Now I will pass it over to Lauren Tesh, who will read the conflict of interest statement.

Conflict of Interest Statement

DR. TESH: The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary

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

Related to the discussion of today's meetings, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 USC Section 208, their employers. These interests may include investments consulting expert witness testimony, contracts, grants, CRADAs, teaching,

speaking, writing, patents, and royalties in primary employment.

Today's agenda involves new drug application 208051 for neratinib maleate, application submitted by Puma Biotechnology. The proposed indication used for this product is as a single agent for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer, who have received prior adjuvant trastuzumab-based therapy.

This is a particular matters meeting, during which the specific matters related to Puma Biotechnology's NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing members, committee members, and temporary voting members to disclose any public statements that they have made concerning the product at issue.

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

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

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

DR. RINI: All right. Thank you, Lauren.

I will now proceed with opening FDA remarks form Dr. Amiri-Kordestani.

Opening Remarks - Laleh Amiri-Kordestani

DR. AMIRI-KORDESTANI: Thank you.

Good morning, chairperson and members of the ODAC, we are here to discuss the neratinib new drug application for proposed indication for the extended adjuvant treatment of adult patients with early-stage HER2-positive breast cancer, who have received prior adjuvant trastuzumab-based therapy.

The applicant, Puma Biotechnology, has requested approval for neratinib based on the results on the extended study and multicenter, randomized, double-blind, placebo-controlled trial of one year of neratinib versus placebo in woman with early-stage HER2-positive breast cancer after adjuvant treatment with trastuzumab.

The primary analysis demonstrated a statistically significant stratified hazard ratio of 0.66, observed with an estimated 2.3 percent absolute difference in invasive disease-free survival at 2 years.

The current standard of care for patients with HER2-positive early breast cancer is

chemotherapy and one year of adjuvant trastuzumab; however, still approximately 15 to 20 percent of patients with HER2-positive early breast cancer will reoccur within 5 years after adjuvant therapy, and there are currently no approved therapies, which improve upon the benefit of trastuzumab for HER2-positive patients in the adjuvant setting.

The neratinib extended adjuvant therapy for breast cancer study results in the context of other FDA approved adjuvant breast cancer therapies has demonstrated a similar rate of benefit in invasive disease-free survival when compared to approvals of adjuvant hormonal therapies, but with a different toxicity profile.

With respect to efficacy, there is uncertainty in the magnitude of treatment effect due to several major amendments made to trial, impacting enrollment, the number of invasive disease-free survival events observed, and the period of patient follow-up. Additionally, there is an imbalance in the number of early dropouts, missing data, and incomplete extending follow-up data.

Ordinarily, in the face of uncertainty, one would draw upon studies from other disease settings, but the information for a metastatic breast cancer and new adjuvant studies with neratinib are not consistent with the results from the extended study.

However, the applicant and the FDA review team have conducted various simulations and exploratory analysis that will be presented later today in detail. These results demonstrated a consistent trend in favor of neratinib.

From a safety standpoint, tolerability in an early-stage setting is a concern. Diarrhea was the most frequently reported adverse reaction in the neratinib arm, with an overall incidence of 95 percent; 40 percent of patients experienced at least one episode of grade 3 diarrhea; 28 percent of patients discontinued neratinib due to an adverse event mainly due to diarrhea.

However, it appears that neratinib can be stopped without long-term sequelae, and results from an ongoing phase 2 study suggest that antidiarrheal prophylaxis decreases the incidence and severity of

diarrhea.

In conclusion, the applicant conducted a randomized, double-blind study of one year of neratinib versus placebo in women with early-stage HER2-positive breast cancer after adjuvant treatment with trastuzumab. The primary analysis at 2 years showed an approximate 2.3 percent improvement in invasive disease-free survival with neratinib treatment.

In order to address uncertainty in the efficacy results, a number of exploratory studies have been performed. These results demonstrated a consistent trend in favor of neratinib; however, given the degree of missing data, the true magnitude of benefit does remain uncertain.

In terms of safety, although there were frequent dose modifications and treatment discontinuations in the neratinib arm mainly due to diarrhea, most toxicities of the drug are non-serious and reversible.

We request the advice of the ODAC on this question, is the risk-benefit profile of neratinib

sufficient to support treatment in the proposed indication? Thank you.

DR. RINI: We will now proceed with the applicant's presentations. Let me just read one statement.

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

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they have with the firm at issue such as consulting fees, travel expenses, honorarium, interests in the sponsor including equity interests and those based on the outcome of this meeting.

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

relationships at the beginning of your presentation, it will not preclude you from speaking.

Applicant Presentation - Alan Auerbach

MR. AUERBACH: Good morning, members of the committee, FDA, members of the patient community, and guests. My name is Alan Auerbach. I am the chief executive officer of Puma Biotechnology. On behalf of Puma, we appreciate the opportunity to share the data with neratinib with you today.

The proposed indication that we are seeking is single-agent therapy for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed or amplified breast cancer, who have received prior adjuvant trastuzumab-based therapy.

Neratinib is an orally available, irreversible, tyrosine kinase inhibitor. It selectively targets members of the ErbB family or receptor tyrosine kinases including HER1, also known as eGFR, HER2, and HER4. Neratinib binds to the intracellular kinase domain of HER1, HER2, and 4 and inhibits signal transduction from these proteins.

This sustained inhibition blocks cell proliferation in cells overexpressing HER2.

The Neratinib Clinical Program encompasses 31 trials, including 11 breast cancer studies with 2000 patient-years' experience. These studies demonstrate neratinib's activity throughout the treatment landscape of HER2-positive breast cancer, including the near adjuvant, extended adjuvant, and metastatic settings.

Our focus today will be the phase 3 ExteNET study and the phase 2 CONTROL study in patients with HER2-positive early-stage breast cancer. These studies are in the extended adjuvant setting, which means one year of continuous therapy with neratinib after patients have completed standard adjuvant therapy with a trastuzumab-based regimen.

In addition to these trials, we have a number of other studies underway in the metastatic setting, and we're committed to the further characterization of the clinical benefit of neratinib in HER2-positive breast cancer.

Our key objectives today are to demonstrate

that there is an unmet medical need for the therapies to further reduce the risk of disease recurrence after adjuvant trastuzumab. ExteNET met its primary endpoint significantly improving invasive disease-free survival at 2 years, and these results were durable out to 5 years. In fact, it is the first trial in HER2-positive breast cancer to demonstrate such a reduction in risk in the extended adjuvant setting.

Neratinib's safety profile is well-characterized, manageable, and predictable, based on data in more than 3,000 patients. The most common adverse event was diarrhea, but it appears with the incidence and severity can be reduced with antidiarrheal prophylaxis. Therefore, we conclude that the benefit-risk profile of neratinib is favorable.

Here you can see the agenda for the rest of the morning's presentation. In addition to our presenters we have other experts here to help address your questions. And now I would like to invite Dr. Jose Baselga to the podium.

Applicant Presentation – Jose Baselga

DR. BASELGA: Thank you all, and I am Jose Baselga from Memorial Sloan Kettering Cancer Center. I am an unpaid consultant for Puma Biotechnology, and I have no financial interest in the outcome of this meeting. I will describe the current tumor landscape for HER2-positive early breast cancer, and place the unmet need into perspective.

Approximately 20 percent of patients diagnosed with breast cancer have HER2-positive disease, which translates in approximately 35,000 patients annually in the United States, and the majority are diagnosed with early-stage disease.

Development of effective adjuvant therapy with anthracyclines, taxanes, and trastuzumab has improved outcomes for a woman with HER2-positive breast cancer. But despite these advances, 15 to 20 percent of patients will recur with invasive breast cancer within 10 years. Once patients develop metastatic disease, which often goes to the liver, brain, and lungs, the prognosis is poor. No therapy has yet proven to be curative for metastatic

HER2-positive breast cancer.

Here, we have the survival data from the recent CLEOPATRA trial, which illustrates outcomes in patients with metastatic HER2-positive disease treated with the best possible care in the first-line setting. These show that the disease is incurable, meaning overall survival in patients treated with trastuzumab, trastuzumab and paclitaxel was about 5 years, and there is no plateau in this course.

Effective adjuvant HER2 targeted therapy is the best opportunity to achieve a cure for those patients with residual disease. Here we have long-term data going out 10 years in patients who were treated with adjuvant chemotherapy with or without trastuzumab for one year from the joint analysis of these two large trials.

In these studies, the protocol-defined endpoint of the effects is the same as invasive diseases survival based on steep criteria, which is generally defined as any local regional, contralateral, ipsilateral, or distant invasive recurrence, or death from any cause.

Disease-free survival was significantly improved with the addition of trastuzumab. Data from these trials had a minimum follow-up of 2 years, together with the data from the HERA trial led to the approval of adjuvant trastuzumab. Similar results were also observed in the BCIRG-006 trial.

Several strategies have been evaluated to try to improve upon the results achieved with adjuvant trastuzumab. One such approach was to treat with trastuzumab for 2 years. Here are our results from the HERA trial that compared one year of trastuzumab shown in red, with 2 years shown by the dashed purple line. Unfortunately, disease-free survival was not improved with longer duration on trastuzumab.

Another strategy is dual HER2 blockade. Here are the results of our large ALTTO trial, which tested the addition of the tyrosine kinase inhibitor, lapatinib, to trastuzumab, and chemotherapy. Concurrent administration of lapatinib and trastuzumab shown in blue improved for year of disease-free survival by 2 percent compared with trastuzumab alone shown in red. Although this was a

promising study, it did not meet the protocol-specified threshold for statistical significance.

Finally, we have the APHINITY trial, which is evaluating the addition of pertuzumab, another HER2 antibody, with known overlapping mechanism of action to standard trastuzumab plus chemotherapy. This trial has been announced to have met its primary endpoint, and the full results will be presented at the ASCO meeting. For full disclosure, I am the co-principal investigator of this trial.

Despite the fact that the APHINITY is positive, it does not solve the problem of recurrences. Therefore, we would agree that more options are needed in this patient population.

Based on the adjuvant studies in HER2-positive breast cancer over the last 5 years, and despite the improved performance of the standard trastuzumab arm in the newer studies, such as ALTTO, it is clear that we are still left with an unmet need.

As shown here, using the data from the

trastuzumab arm of the ALTTO study, approximately 15 percent of patients will have a disease-free survival event within 5 years, and their risk continues well beyond that.

Moreover, we've seen that within the population, there are patients with high-risk disease who have a worse prognosis. These are data from the BCRIG-006 trial showing that patients with node-positive disease have substantially lower 5-year disease-free survival rates than patients with node-negative disease.

What is the rationale for using neratinib in the extended adjuvant setting? First, it is known that heterodimerization of HER2 with other HER2 family members provides mechanisms to escape inhibition by trastuzumab. In this setting, neratinib, which is a potent irreversible pan-HER inhibitor, has been shown to be non-cross-resistant with trastuzumab in metastatic HER2-positive breast cancer. Neratinib has a different mechanism of action than the anti-HER2 antibodies and is more potent than lapatinib. Therefore, it may overcome

resistance and provide more complete blockade of HER2 signaling.

Finally, this approach of adding a second agent with a different mechanism of action after standard adjuvant therapy has been shown to be effective in hormone receptor-positive breast cancer.

In summary, HER2-positive breast cancer is an aggressive disease, and when it's metastasized it is associated with poor prognosis. Therefore, effective adjuvant therapy is the best opportunity for a cure, but with current standard therapy a substantial proportion of patients remain at risk. This has perked ongoing research to find more effective adjuvant regimes that include novel HER2 targeted agents, such a neratinib and trastuzumab.

Neratinib is a potent irreversible pan-HER inhibitor with proven activity in the metastatic setting that is non-cross-resistant with trastuzumab, so there is a strong biological rationale for neratinib in the extended adjuvant setting.

Now I would like to invite Dr. Alvin Wong to the podium to describe the neratinib clinical

program. Alvin?

Applicant Presentation - Alvin Wong

DR. WONG: Thank you, Dr. Baselga.

Good morning. My name is Alvin Wong. I'm vice president of clinical science and pharmacology at Puma Biotechnology. I'm pleased to present the important data from the Neratinib Clinical Development Program. As background, I'll first cover pharmacology and dose selection. Next, I'll cover the activity in metastatic and neoadjuvant setting. And finally, I'll present the data in the pivotal trial in the extended adjuvant setting.

The clinical pharmacology of neratinib has been studied extensively. It has a terminal elimination half-life of 10 to 15 hours with a linear PK allowing once-a-day dosing without accumulation. Similar to other TKIs, neratinib is predominantly metabolized in the liver by cytochrome P450 3A4 and inhibits P-glycoprotein. Therefore, reviewing the patient's concomitant medications for potential interactions is important.

Phase 1 and 2 studies in patients with

metastatic disease established the 240-milligram once-daily dosing as a recommended dose that was used in the ExteNET. Study 102 of phase 1 dose-finding study determined that MTD of 320 milligrams and the DLT was diarrhea. Then in study 200, the dose was reduced to 240 milligrams because of a high rate of grade 3-4 treatment-related diarrhea at the 320-milligram dose; whereas at 240, 23 percent of patients had grade 3 or 4 diarrhea, and only 2 percent discontinued.

In patients with metastatic HER2-positive disease, neratinib is highly active. Single-agent neratinib had an overall response rate of 25 to 29 percent in patients previously treated with trastuzumab and 54 percent in trastuzumab-naive patients.

Neratinib also has been studied in combination with chemotherapy. In study 3005, a randomized trial in the first-line setting, neratinib plus paclitaxel demonstrated similar response rates compared to trastuzumab plus paclitaxel, and the median progression-free survival was 13 months in

both arms. In addition, neratinib reduced the frequency of symptomatic and progressive CNS recurrences.

Neratinib also demonstrated a favorable activity compared to trastuzumab in the neoadjuvant setting. In I-SPY 2, patients were randomized to neratinib plus chemotherapy or trastuzumab plus chemotherapy. In women with HER2-positive disease, the pathologic complete response rate was 39 percent in the neratinib arm versus 23 with trastuzumab. Neratinib also achieved higher PCR rates than trastuzumab in both hormone receptor-positive and negative subgroups.

Together with the data from the metastatic settings, these results support the scientific rationale for neratinib in the adjuvant setting.

The pivotal ExteNET study in the extended adjuvant setting enrolled 2,840 women with early-stage HER2-positive breast cancer, which was determined locally by IHC or ISH. Eligible patients had to have stage 1 through 3c disease, had completed prior adjuvant therapy with trastuzumab within

2 years, and could be either hormone receptor-positive or negative.

Patients were randomized one-to-one to receive neratinib or placebo for one year. The primary endpoint is invasive disease-free survival as defined by modified steep criteria the current standard endpoint in adjuvant breast cancer trials.

All invasive disease survival events up to the cutoff date of 2 years plus 28 days were included in the primary analysis. Secondary endpoints and prespecified stratification factors are shown here. Stratification factors were selected based on standard prognostic risk factors in breast cancer patients. The study was blinded until the primary analysis at 2 years, and survival remains blinded. The trial was amended to include a preplanned 5-year iDFS analysis and overall survival analysis.

I will now show the history of the study. ExteNET evolved over time and has had three different sponsors. Under Wyeth, the academic steering committee designed the study to enroll 3,850 patients with node-positive or negative disease. The primary

endpoint was an event-driven analysis of invasive disease-free survival at 337 events. Patients were followed for about approximately 5 years.

After Pfizer acquired Wyeth, data from the joint analysis of the trastuzumab approval trial showed that the risk of recurrence is highest within the first year after completing adjuvant trastuzumab, and patients with node-negative disease had a lower recurrence rate. The trial was amended to focus on the higher risk patients with node-positive disease, who had completed adjuvant trastuzumab less than one year from study entry; this was called the amended ITT.

In 2011, Pfizer made a business decision to halt the enrollment at 2,840 patients and truncated follow-up at 2 years. This was not driven by an interim analysis or any communication from the IDMC.

After Puma acquired neratinib, the 2-year HERA results became available and confirmed the one-year trastuzumab as a standard regimen, then I-SPY 2 showed that neratinib was superior to trastuzumab in neoadjuvant therapy.

This caused us to re-evaluate the importance of ExteNET, so we brought in independent experts in statistics and study design, who recommended bringing the study back to its original intent. We amended ExteNET in January 2014, to restore the original ITT analysis population and 5 years of follow-up. However, we had to maintain the primary iDFS analysis using data only from the first 2 years due to protocol mandated assessments during that time. The majority of patients had reached 2 years and were off study. The 5-year iDFS analysis was added to assess durability.

It is important to note that the study remained blinded throughout this process. The study was finally unblinded, and the primary iDFS analysis in July 2014, death events remained blinded.

Throughout the trial, the sponsor has taken measures to maintain the integrity of the trial. First, the infrastructure for the study conduct was consistent with the Independent Data Monitoring Committee, Independent Statistical CRO, and consistent study monitoring plans. The sponsor in

the clinical sites were blinded to treatment assignments during all of the amendments and prior to the iDFS analysis, and the sponsor in the clinical sites still are blinded for assignments for overall survival. The Academic Steering Committee provided scientific oversite for the trial.

This is an overview of the statistical analysis plan. For the primary analysis, the hypothesized hazard ratio was 0.667, and we used a stratified log-rank test with a two-sided alpha equal to 0.05 and a Cox proportional hazards model.

Overall survival is a secondary endpoint and will be tested after 248 events have been reached. The 5-year iDFS and the secondary endpoints at 2 and 5 years are descriptive. All were pre-specified to support the primary analysis and the durability of the treatment effect.

This slide summarizes the assessments of recurrence. During the first year on treatment, patients received a full history and physical exam at the beginning and end of study treatment. Symptom-guided history physical exams were done

during the scheduled visits at baseline, months 1, 3, 6, and 9. Women also received a mammogram every 12 months. In year 2, these scheduled visits were every 4 months.

In years 3 to 5, patients were followed per standard of care, typically, twice a year according to national guidelines. All disease recurrences were based on history and physical exams and were confirmed either by biopsy or radiographic evidence of metastatic disease.

Patient demographics were well-balanced between treatment groups with respect to region, menopausal status, and trastuzumab regimen. The median time from completion of adjuvant trastuzumab was 4 and a half months.

Baseline characteristics were also well-balanced between treatment groups. Approximately three-quarters of patients were node-positive, a little more than half were hormone receptor-positive, and among hormone receptor-positive patients, 93 percent received concomitant endocrine therapy. Both arms were

well-balanced with respect to prior adjuvant therapy; and now the primary efficacy results.

Our trial met its primary endpoint of invasive disease-free survival. Neratinib demonstrated a hazard ratio of 0.66, which represents a 34 percent relative reduction in risk of recurrence with a statistically significant two-sided p-value of 0.008. The absolute improvement was 2.3 percent at 2 years. The censoring observed at 24 months was due to the timing of the assessments, and it improved with longer follow-up.

ExteNET is the first trial to show a significant reduction in the risk of recurrence beyond what was achieved with one year of adjuvant trastuzumab. With respect to the sites of recurrence, a total of 173 DFS events had occurred, 67 in the neratinib arm and 106 in the placebo. The majority of the invasive disease events were distant recurrences, and that's where we saw the greatest reduction in events in the neratinib arm. In total, there were 59 patients within the neratinib arm versus 96 in the placebo arm with local, regional, or

distant recurrences.

Each of the prespecified secondary endpoints also favored neratinib with hazard ratios ranging from 0.61 to 0.74. All of these except for overall survival were analyzed based on the 2-year primary data. The survival analysis has not yet matured.

We also analyzed iDFS based on the stratification factors by nodes, hormone receptor status, and trastuzumab regimen. The forest plot demonstrates that all the point estimates are in favor of the neratinib arm.

The only subgroup that demonstrates a significant treatment interaction was the hormone receptor status with a descriptive p-value of 0.045. When we looked at the subgroup by hormone receptor status, we saw that the hormone receptors-positive subgroup has a hazard ratio of 0.49 with an absolute benefit of 4.1 percent at 2 years. In contrast, the hormone receptor-negative subgroup, although the curve separated at 12 months, they began to come together after treatment was stopped; the hazard ratio was 0.93.

It's important to keep in mind that these are exploratory analyses, and should be interpreted with caution.

As I mentioned previously, in an effort to restore the trial to its original design, the study was amended to include a full 5 years of follow-up. We reached out to 100 percent of the centers and requested that they reconsent their patients, most of whom were still being seen by their study doctors for routine follow-up.

As of March 2017, we have successfully reconsented 2,117 patients, which represents approximately 76 percent of available patients. With the 5 years of follow-up the Kaplan-Meier curve showed that the iDFS benefit of neratinib is durable. This preplanned analysis demonstrated a descriptive hazard ratio of 0.73 with a two-sided p-value of 0.008 and an absolute DFS benefit at 2.5 percent at 5 years.

In addition, the early censoring observed in the primary analysis has been addressed by the reconsented patients. We now have 79 percent of

patients at 24 months, up from 48 percent in the primary analysis. Similar to what we saw on the 2-year data, the majority of the DFS events were distant recurrences and the supported efficacy was maintained in the secondary endpoints.

The analysis of the prespecified subgroups based on the 5-year data is consistent with the analysis at 2 years. Because of the increased number of patients at risk, the confidence intervals have narrowed compared to the 2-year analysis.

The subgroup analysis by hormone receptor status at 5 years is consistent with the primary analysis at 2 years. The treatment effect on the hormone receptor-positive patients continued to improve with longer follow-up. However, in the HR-negative subgroup, the curves converged after 2 years.

In summary, the ExteNET is the first trial to show a clinically meaningful, statistically significant reduction in the risk of recurrence with women with HER2-positive early breast cancer, who received prior adjuvant trastuzumab-based therapy.

The benefit is supported by the secondary endpoints and exploratory subgroups suggesting that there may be a difference in the magnitude of benefit on hormone receptor status.

The updated analysis is consistent with the primary analysis and demonstrated that the benefit is durable out to 5 years. These data are further supported by activity in other settings. We are confident that the totality of the data demonstrates that the extended adjuvant therapy with neratinib significantly improves disease-free survival in the adjuvant setting.

Now I'd like to invite Dr. Susan Moran to share our safety data.

Applicant Presentation - Susan Moran

DR. MORAN: Thank you, Dr. Wong.

Good morning. My name is Susan Moran. I'm vice president of clinical development at Puma Biotechnology. This morning I'll present data regarding the tolerability profile of neratinib in the extended adjuvant setting.

The safety of neratinib has been extensively

evaluated with the safety database of over 3,000 cancer patients. Its safety profile is consistent, and diarrhea is the most common and predictable adverse event.

Neratinib-associated diarrhea has a distinct clinical course. It occurs early after neratinib initiation, and severe diarrhea is generally short-lived and infrequently leads to dehydration or need for hospitalization. Other than diarrhea, there is a low incidence of severe or serious adverse events and importantly no cumulative toxicity associated with neratinib.

In a moment, I will review data from the pivotal ExteNET study, and later Dr. Rugo will share data from our ongoing phase 2 study, the CONTROL trial, designed to mitigate the primary tolerability concern associated with neratinib.

In ExteNET, median duration of treatment was 11.6 and 11.8 months in the neratinib and placebo arms respectively. The mean duration of treatment was shorter in the neratinib arm as a result of premature treatment discontinuations. Mean actual

and relative dose intensity was also lower in the neratinib arm as a result of dose reductions.

Overall adverse events, severe adverse events, and adverse events leading to dose modification and discontinuation were reported more frequently in the neratinib than placebo arm. Severe adverse events and adverse events leading to dose modification and discontinuation were largely related to diarrhea.

For the most part, the safety profile of neratinib is typical for tyrosine kinase inhibitors that inhibit eGFR. In the ExteNET study, where no antidiarrheal prophylaxis was incorporated, gastrointestinal adverse events, specifically diarrhea, nausea, vomiting, and abdominal pain, were reported more frequently in the neratinib than placebo arm.

With respect to grade 3 or 4 adverse events, the most common event was diarrhea. Other than diarrhea and vomiting, all other severe adverse events occurred at an incidence of less than 2 percent. And importantly, there's a low incidence

of severe elevations of liver transaminases and no evidence of neratinib-associated bone marrow or cardiotoxicity.

Diarrhea was the most common adverse event leading to treatment discontinuation or dose reduction. In the neratinib arm 16.8 percent of patients discontinued and 26.4 percent had at least one dose reduction due to diarrhea.

As I mentioned earlier, neratinib-associated diarrhea has a distinct clinical course. Diarrhea usually occurs within the first week, with a median time to onset of 2 days. Grade 3 events tend to occur at the end of the first week, with median time to onset of 8 days. Episodes of grade 2 and 3 diarrhea are generally short, and for most patients not recurrent. Patients experienced a median of 3 episodes of grade 2 or higher, and 2 episodes of grade 3 diarrhea over the course of a year.

Cumulative duration of grade 2 or higher diarrhea was 10 days over the course of a year, compared to 5 days for grade 3, and there were very few events that lead to hospitalization.

So what we've learned is that although some patients experience severe diarrhea, it occurs early, is generally of short duration, and infrequently leads to complications requiring hospitalization.

Because diarrhea episodes are of short duration, the incidence of adverse events that might be indicative of complications is low. Less than 1 percent of neratinib patients experienced severe dehydration, nephrotoxicity, electrolyte abnormalities, or weight loss. All nephrotoxicity events were related to elevations in serum creatinine in the setting of pre-renal volume depletion, and all were reversible with hydration, study drug interruption, or discontinuation.

In summary, the overall safety profile of neratinib at a dose of 240 milligrams per day is well-characterized based on more than 3,000 cancer patients. Overall, with the exception of diarrhea, neratinib is associated with a low incidence of severe adverse events. Diarrhea associated with neratinib is common and leads to a high rate of premature discontinuation. However, severe diarrhea

is generally of short duration and infrequently leads to severe or serious complications. For patients who stay on therapy after month 1, tolerability is improved. Overall, neratinib has a manageable safety profile.

Now I would like to discuss the effects of antidiarrheal prophylaxis. After Puma acquired neratinib, 1 month of loperamide antidiarrheal prophylaxis was incorporated in all neratinib trials. Here we see the incidence of severe diarrhea in the ExteNET study without loperamide prophylaxis, and now on the right we see the results of two Puma studies of neratinib in patients with solid tumors where loperamide prophylaxis reduced the incidence of grade 3 diarrhea.

The effectiveness of loperamide prophylaxis in the advanced cancer setting led us to believe that this strategy would work well in the extended adjuvant setting.

We've also conducted preclinical investigations to further identify the etiology of neratinib-associated diarrhea. Preclinical models

suggest the etiology is multifactorial, including elements of secretory and inflammatory diarrhea. And in particular, in a rat model, we observed inflammation in the terminal ilium.

As a result, we are studying other antidiarrheal agents in combination with loperamide. These include budesonide, a locally acting corticosteroid used in inflammatory GI conditions, and colestipol, a bile acid sequestrant. Both of these agents were effective in reducing diarrhea in the rat model.

Study 6201, or the CONTROL trial, is an ongoing study to investigate the effectiveness of 1 to 2 months of antidiarrheal therapy in the extended adjuvant setting. The study is a covered study in the context of the NDA and provides important information on the impact of antidiarrheal prophylaxis on the tolerability of neratinib. Based on this study, we are recommending 1 to 2 months of antidiarrheal prophylaxis in our draft label.

Based on the effectiveness of loperamide in reducing severe diarrhea in the advanced cancer

setting, the first cohort tested loperamide in combination with neratinib for the first 2 months of neratinib treatment. The second cohort tested 1 month of budesonide added to the 2-month loperamide regimen. And finally, we are currently enrolling into a cohort testing colestipol added to loperamide both for 1 month.

The loperamide data are most mature with 9 months median time on study. The budesonide cohort recently completed enrollment, and median time on study was 3 months. All patients have had the opportunity to complete at least 1 month of therapy, and therefore, we are confident in these data because most events of severe diarrhea and premature discontinuations occur in the first month.

The colestipol cohort is the newest cohort, and the median time on study was less than 1 month at the time of this analysis. We look forward to sharing these data when they are more mature.

Now I would like to invite Dr. Rugo to share preliminary data from the ongoing CONTROL study and also to provide her perspective on the tolerability

of neratinib-associated diarrhea.

Applicant Presentation - Hope Rugo

DR. RUGO: Thank you, Susan.

I'm Hope Rugo from the University of California San Francisco. I'm an unpaid consultant to Puma, and I have no financial interest in the outcome of this meeting. I'd like to offer my clinical perspective with regard to the tolerability of adjuvant therapies for breast cancer and the diarrhea associated with neratinib.

I'm an investigator in the CONTROL study, so I have seen first-hand that antidiarrheal prophylaxis can reduce the incidence and severity of neratinib-associated diarrhea. Diarrhea is a common toxicity of cancer treatment, and the diarrhea associated with neratinib is manageable and is similar to what we see with other agents.

In particular, I want to stress that the clinical course of neratinib-associated diarrhea is quite distinct and reproducible. It almost always occurs right away within the first week of therapy and typically diminishes with time. It is usually

with short duration lasting 1 to 2 days, and once it is under control, it usually doesn't recur.

What we found is that antidiarrheal prophylaxis for the first 2 cycles followed by loperamide as needed is very effective. And when coupled with dose modification and patient education, we can keep our patients on therapy. It is important to talk to patients and make sure that they understand the diarrhea is short-lived and won't persist if managed proactively.

Here is a summary of the data from the ExteNET study where no antidiarrheal prophylaxis was incorporated. Green indicates no diarrhea, yellow grade 1, orange grade 2, and purple grade 3 diarrhea as the worst grade experienced.

When we compare these data with the CONTROL study, we see that loperamide prophylaxis reduces the incidence of grade 3 diarrhea and increases the proportion of patients with no diarrhea. In addition, it appears that the addition of budesonide further reduces the incidence of grade 3 diarrhea.

Given that the follow-up is different between

these cohorts and most of the diarrhea occurs in the first month, we compared the incidence of diarrhea in month 1 between these cohorts. This analysis confirms that prophylaxis can markedly reduce the incidence and severity of diarrhea.

In these 1-month pie charts, you can see in particular that if you look at the green and orange combined, that the amount of the pie increases with the addition of loperamide and then with the combination of budesonide and loperamide. Therefore, Puma is recommending antidiarrheal prophylaxis with neratinib therapy.

Prophylaxis also improves neratinib tolerability. Prophylaxis is associated with a decreased incidence of diarrhea-related adverse events leading to dose hold and dose reduction. In addition, the rate of discontinuation due to diarrhea was substantially lower in the budesonide cohort.

Although the discontinuation rate in the loperamide cohort of CONTROL was higher than expected early on, it declined as the investigators became more familiar with neratinib.

Loperamide prophylaxis also reduces the cumulative duration of diarrhea regardless of grade. The median cumulative duration of all-grade diarrhea was 59 days in the ExteNET. In the loperamide arm of CONTROL, the median duration was just 12 days. The median duration of diarrhea was 6 days in the budesonide arm, although these data are less mature. The median duration of grade 3 diarrhea was 5 days in ExteNET and decreased to 3 days in the loperamide and budesonide cohorts.

Of note, if we look at just the first month of treatment, the data looked very similar. Clearly, prophylaxis reduces the burden of diarrhea. We are continuing to study this area to identify the optimal prophylactic regimen.

To put these data into perspective, here is a list of other HER2 targeted agents and regimens and the reported incidence of diarrhea. For example, in data just presented at San Antonio, we see that the combination of pertuzumab with docetaxel, carboplatin, and trastuzumab in the neoadjuvant setting resulted in grade 3 diarrhea in 23 percent of

patients, similar to what we saw in the CONTROL trial with loperamide prophylaxis.

The other challenge in adjuvant trials is to keep patients on treatment. It's not uncommon to have 20 to 30 percent of patients drop out of adjuvant trials with the most common reason being tolerability. Tolerability is clearly an important factor that affects adherence, particularly with oral medications. The ongoing CONTROL trial is designed to address this issue.

In summary, neratinib-associated diarrhea typically occurs early and diminishes with time and is manageable with antidiarrheal prophylaxis and patient education. The data from the CONTROL trial show that prophylaxis improves tolerability and reduces both the incidence and severity of neratinib-associated diarrhea.

Diarrhea is a common side effect of adjuvant therapies for HER2-positive breast cancer. Therefore, we have to manage diarrhea proactively because more than any other side effect, it affects tolerability, which is important for adherence to

therapy.

Thank you very much, and I'd like to invite my colleague Dr. Joyce O'Shaughnessy to the podium.

Applicant Presentation - Joyce O'Shaughnessy

DR. O'SHAUGHNESSY: Thank you, Dr. Rugo.

My name is Joyce O'Shaughnessy from Baylor University Medical Center in Dallas. I was an investigator in ExteNET, and I'm a paid consultant for Puma Biotechnology. I have no financial interest in the outcome of this meeting.

I would like to offer my clinical perspective on the benefits and risk of neratinib in the extended adjuvant setting. The outcome for patients with early-stage HER2-positive breast cancer has dramatically improved over the last 20 years. In the 1990s, 5-year disease-free survival rates with anthracycline-based chemotherapy alone were only 50 percent.

With the addition of taxanes to anthracycline-based regimens, 5-year disease-free survival improved to 74 percent. The addition of concurrent trastuzumab to adjuvant chemotherapy

improved 5-year disease-free survival to about 85 percent, and that is the current standard of care.

Now, with the extended adjuvant neratinib, we appear to have further improved the 5-year disease-free survival to about 90 percent. Of course, such cross-trial comparisons have limitations; and as you can see, the CONTROL arm in ExteNET performed slightly better than the trastuzumab arm in N-9831. But I think it's clear that neratinib further improves patient outcomes over the current standard of care.

How does the disease-free survival benefit seen with neratinib compare to other adjuvant therapies? Shown here are the data that lead to approval of other breast cancer adjuvant therapies based on median follow-up durations ranging from 2 to 5.8 years.

If we look at the hazard ratios that range from 0.87 to 0.48, the relative risk reductions range from 13 percent with anastrozole to 52 percent with trastuzumab, so the 34 percent relative risk reduction observed in ExteNET is well within this

previously established range.

With regard to the absolute 2-year and 5-year outcomes, neratinib benefit is comparable to what has been seen with adjuvant endocrine therapies. Of note, the placebo-controlled MA-17 trial of letrozole in the extended adjuvant setting showed a very similar magnitude of benefit, as did ExteNET.

As a clinician, I feel it is very important that I consider offering my patients every adjuvant therapy that is a proven benefit in the curative setting. With regard to neratinib, it is very clear to me, as it will be to my patients, that a 34 percent relative reduction in the risk of breast cancer recurrence or death is highly clinically meaningful.

Importantly, the improvement in disease-free survival seen at 2 years holds up over time with patients still having substantial benefit at 5 years, having been treated with neratinib for only one year. Neratinib is a unique agent that I need as an option in my practice because pan-HER inhibition will prevent recurrence in some patients whose disease was

not eradicated by adjuvant trastuzumab.

With regard to the risks of neratinib, I am confident that the toxicity and safety issues have been well-characterized given the over 2,000 patient-years experience with neratinib and breast cancer. I believe that the risks associated with neratinib are acceptable in the curative setting.

Patients do not need to worry about cardiac or bone marrow toxicity, nor about hair loss or neuropathy with neratinib. However, I do have to tell my patients in detail how to proactively prevent serious diarrhea from developing, emphasizing the need to call us if they have substantial diarrhea. I fully agree with Dr. Rugo that we have the tools we need to prevent and reduce neratinib-associated diarrhea.

In conclusion, although significant advances have been made in treating HER2-positive breast cancer, patients remain at risk for recurrence and death after adjuvant trastuzumab. Neratinib provides a clinically meaningful, durable reduction in that risk, and we don't have any other agents that can do

this. Neratinib's safety profile is well-characterized, predictable, and manageable, and we are well prepared to address the diarrhea.

Given everything we've heard today, and my personal experience using neratinib in ExteNET, I'm convinced that the benefit of neratinib greatly outweighs the risk. I want to have access toward neratinib in my practice, and I very much hope that the panel will support its approval.

Thank you very much, and we look forward to your comments and discussion.

DR. RINI: Okay, thank you to the sponsor for that nice presentation. We'll now proceed with presentations from FDA.

FDA Presentation - Harpreet Singh

DR. SINGH: Thank you members of the advisory committee, colleagues, ladies, and gentlemen. My name is Harpreet Singh, and I am going to present the clinical portion of the FDA analysis of the neratinib NDA.

My presentation will be followed by the FDA's statistical analysis by Dr. Joyce Cheng, and

Dr. Amanda Walker will provide a safety and tolerability analysis and discuss our conclusions. The members of the FDA review team are shown on this slide.

The proposed indication for neratinib is for the extended adjuvant setting in patients with early-stage HER2-positive breast cancer who have completed a year of trastuzumab therapy.

Today we will discuss the benefit-risk profile of neratinib. The ExteNET study demonstrated that extended adjuvant therapy with one year of neratinib after completion of one year of adjuvant trastuzumab, resulted in a 2.3 percent improvement in disease-free survival at 2 years. We aim to facilitate a discussion of this demonstrated benefit in the context of the safety and tolerability data for this agent in an early breast cancer setting.

You will hear about adaptations to the ExteNET study design over the course of the drugs development program, which created uncertainty around the magnitude of benefit. Multiple statistical analyses were performed to address these concerns,

which demonstrated a consistent effect of neratinib.

We will also discuss the totality of evidence of neratinib's efficacy data, both in the context of prior FDA adjuvant approvals, and of the drugs overall development program, in which there have been inconsistencies in which populations benefit from this therapy.

The current standard of care for early-stage HER2-positive breast cancer patients is adjuvant chemotherapy plus a year of trastuzumab. However, about 20 percent of these patients relapse within 5 years. There are currently no approved therapies, which improve upon the benefits of trastuzumab for HER2-positive patients in the adjuvant setting.

Extended adjuvant treatment was studied in the HERA trial, which randomized over 5,000 women with HER2-positive early-stage breast cancer to 1 year of trastuzumab versus 2 years versus observation with disease-free survival and overall survival as endpoints. The study was event-driven and showed no difference in either disease-free survival or overall survival for one year of

trastuzumab versus two.

However, when evaluating the Kaplan-Meier curves, at the 2-year time point, it appears that 2 years of trastuzumab may improve disease-free survival. With extended follow-up, this perceived benefit disappears. These results call into question whether 2 years of follow-up, as seen in the ExteNET trial, is adequate to capture the natural history of HER2-positive breast cancer.

We reviewed all FDA approved adjuvant breast cancer therapy since 1999. These drugs included traditional chemotherapy, hormonal therapies, and one HER2 targeted drug, trastuzumab. A full listing of these approvals is included in the briefing document.

Most used an active comparator or add-on design with one prior approval based on a placebo-controlled trial. The median follow-up ranged from 24 months to over 5 years with absolute improvements in disease-free survival ranging from 1.8 percent, with the approval of letrozole in 2005, to 9 percent.

Trastuzumab is the only approved adjuvant

therapy for HER2-positive breast cancer and was approved in 2006, based on a 6.7 percent improvement in disease-free survival with a hazard ratio of 0.48. Many prior approved therapies also demonstrated overall survival benefit at the time of approval or shortly thereafter, and all had prior FDA approvals in the metastatic setting at the time of their adjuvant approval.

Here are a few additional points to consider with ExteNET in the context of prior adjuvant approvals. It should be noted that neratinib should not be directly compared to prior adjuvant approvals given the various disease settings, however are discussed here to provide context.

The ExteNET trial had a lower number of disease-free survival events in the extended adjuvant setting compared to prior approvals. It is not clear whether this is due to the extended nature of the study and that a higher number of events would be anticipated prior to the initiation of neratinib.

Next, the use of placebo control in comparison to an active comparator makes a difference

in the magnitude of benefit, as well as the hazard ratio, which one would expect. The 2.3 percent improvement in disease-free survival at 2 years is similar to early approvals of hormonal and chemotherapies, but with a different safety profile and tolerability profile, which you will hear about later in the presentation.

Several clinical trials have been conducted using neratinib as monotherapy and in combination with other agents in the neoadjuvant and metastatic breast cancer settings. Two neoadjuvant trials were conducted by cooperative groups evaluating neratinib with pathologic complete response as their primary endpoint.

In both trials, patients with hormone receptor-negative tumors appeared to derive greater benefit than those with hormone receptor-positive tumors. This finding is in contrast to ExteNET, in which there appears to be a differential treatment affect in disease-free survival favoring those with hormone receptor-positive tumors. This may be due to a potential crosstalk between estrogen receptor and

HER2 pathways.

Studies 3003 and 3005 were conducted in the metastatic setting comparing neratinib monotherapy to lapatinib and capecitabine, and comparing neratinib versus trastuzumab with chemotherapy. While neratinib did show activity in these trials, based on response rate data, neither of these studies met their primary endpoint.

We will now discuss the ExteNET study design and major amendments. As discussed, the drug development program evolved through three different sponsors. This design represents the final iteration, however, there were major changes throughout the study.

Patients were randomized one-to-one to neratinib versus placebo with one year, with a primary endpoint of invasive disease-free survival. Stratification factors are shown. There are three parts to the study; one being the 2-year invasive disease-free survival as the primary analysis; the next is an expanded follow-up to obtain durability of 2-year disease-free survival results; and the

extended follow-up portion aims to collect overall survival data. These were the results of major amendments.

At the time of study initiation, Wyeth planned to follow patients for 5 years using an event-driven analysis. The first major amendment under Pfizer enriched the ITT population to make it more high-risk excluding those with stage 1 and/or node-negative disease, and within one year of trastuzumab treatment instead of two. This was to increase the likelihood of success of the trial based on data from adjuvant trastuzumab trials, which show a higher risk of recurrence closer to completion of trastuzumab.

Next, due to organizational changes, enrollment was stopped and follow-up was truncated from 5 years to 2 years. The analysis was changed from event-driven to time-driven.

The last major amendment came when Puma took over. First, the primary analysis was reverted back to the ITT population. In an effort to gain additional disease-free survival and overall survival

data, the study follow-up period was extended to 5 years, and patients were reconsented to obtain survival data from their medical records.

The applicant's decision to attempt reconsent of all patients for extended follow-up data was driven by advice they received from outside statistical consultants.

The major amendments resulted in multiple adaptations to the statistical analysis plan, which will be addressed by our bio-statistical reviewer. This included changes in sample size, shift from an event-driven to a time-driven analysis, and missing data in the extended follow-up period. The major changes in the protocol were reported to be the result of outside factors, such as external information and changes in organizational strategy.

We will now discuss the results of the ExteNET trial. Though not shown here, baseline factors were well-balanced in terms of demographics and disease characteristics. Patient disposition is shown. Of note, 26 percent of patients discontinued treatment due to adverse events compared with

5 percent of patients on the placebo arm. Also, the overall withdrawal rate was 21 percent in the neratinib arm versus 15 percent in the placebo group.

Next, Dr. Joyce Cheng will present the FDA statistical analysis of the ExteNET trial.

FDA Presentation – Joyce Cheng

DR. CHENG: Thanks, Harpreet.

Good morning. My name is Joyce Cheng, and I am the primary statistical reviewer for this application. Here is an outline of my presentation today.

First, I'm going to take you through the efficacy results from ExteNET, which have already been presented by the applicant. The primary analysis showed a statistically significant treatment effect favoring neratinib. I will then discuss the impact of the major amendments on the interpretation of the results.

Second, I'll discuss results from additional sensitivity analyses the FDA conducted to address statistical issues that came up during review. These included a simulation to address early dropouts in

the primary analysis and a tipping-point analysis to address missing data in the extended follow-up collected. All will show an effect in favor of neratinib.

We will also look at results from some exploratory subgroup analyses. Lastly, I'll end with a summary of our statistical conclusions.

Here are the primary efficacy results from ExteNET. The primary analysis of iDFS was conducted with the follow-up period of 2 years. The Kaplan-Meier plot is shown here. The event rate on the neratinib arm was 4.7 percent compared to 7.5 percent on the placebo arm. The treatment effect was statistically significant with a stratified hazard ratio of 0.66. The Kaplan-Meier estimate of disease-free survival rate at 2 years was 94.2 percent on the neratinib arm compared to 91.9 percent on the placebo arm for an absolute difference of 2.3 percent.

As described before, there were multiple amendments to the study, which resulted in the primary analysis being conducted with 2 years of

follow-up truncated from 5 years in a time-driven rather than event-driven analysis. Because of the 2-year truncation, the applicant implemented a reconsent process to obtain extended follow-up for patients for 5 years post-randomization.

The applicant has stated that all changes made to the study were due to external information. Thus, our conclusion is that these changes were unlikely to have impact on the control of type 1 error rate.

After implementing the reconsent process, the applicant was able to reconsent 75 percent of the ITT patients consisting of 1,028 neratinib patients and 1,089 placebo patients. Baseline characteristics were well-balanced between the two arms among those reconsented.

With the extended follow-up data collected from these patients, the applicant conducted an exploratory updated analysis of iDFS with follow-up again truncated at 2 years. This analysis included an additional 17 events across both arms. Results from the updated 2-year analysis were consistent with

what was seen in the primary analysis, with a stratified hazard ratio of 0.68.

The applicant also conducted an exploratory analysis of iDFS with up to 5 years of follow-up. Again, this was based on data collected after 75 percent of patients were reconsented. The Kaplan-Meier plot is shown here.

The event rate was 8.2 percent on the neratinib arm compared to 11.5 percent on the placebo arm. The hazard ratio was 0.73, and the initial 2-year difference seen in the primary analysis appears to be sustained for up to 5 years in this analysis.

To summarize, the efficacy results from ExteNET were as follows; the primary analysis of iDFS with 2 years of follow-up observed the statistically significant stratified hazard ratio of 0.66. The updated 2-year analysis observed a stratified hazard ratio of 0.68, consistent with the primary analysis. The updated analysis with up to 5 years of follow-up observed a stratified hazard ratio of 0.73. We note that additional data appears to cause the hazard

ratio estimate to increase.

In the FDA's analysis of the data, we observed an imbalance of early dropouts, as well as missing data due to an incomplete reconsent process. The FDA sensitivity analyses conducted were designed to address these issues. Further, exploratory subgroup analyses were conducted for the stratification factors.

First, we consider the imbalance of early dropouts in the primary analysis. There were a larger number of patients with iDFS times censored before 3 months on the neratinib arm, compared to the placebo arm.

In the primary analysis, there are 130 neratinib early dropouts compared to 44 placebo. After extended follow-up data was collected, these numbers dropped down to 80 neratinib versus 25 placebo in the updated 2-year analysis. The most common reasons for these neratinib early dropouts were adverse event and subject request. The censoring of these patients' iDFS times could be informative since they dropped out due to

treatment-related toxicity. In general, informative censoring can have an impact on results. Therefore, the FDA conducted a simulation with imputation to assess the impact of early dropouts.

Results from the simulation are shown in the table here. Across simulated trials, the average stratified hazard ratio was 0.69, and the average difference in 2-year iDFS rates was 2.5 percent. The primary analysis observed a stratified hazard ratio of 0.66 and a 2.3 percent difference in 2-year iDFS rates. Thus, the results after imputation for the neratinib early dropouts were similar to the results from the primary analysis.

We also want to address the missing data in the extended follow-up collected. Note, that the last patient was randomized into the study in 2011. We determined that a total of 754 patients had missing data. Among the patients who are not reconsented, 622 had iDFS times that were censored. Among the patients who were reconsented, 132 had iDFS times that were still censored prior to 5 years. Due to missing data, it is unknown how many of these

patients recur within 5 years. The number of events that occur among these patients could have an impact on results.

To evaluate the impact of the missing data that exists, a tipping-point analysis was conducted. In general terms, a tipping-point analysis is a sensitivity analysis with imputation that searches for a tipping-point that will reverse the study's conclusion.

In this case, the tipping-point analysis seeks to determine the rate at which events need to occur on the neratinib arm in order to reverse significance with a p-value greater than 0.05. We determined that the tipping-point is reached when the rate of new neratinib events was 8.4 percent. This event rate of 8.4 percent is high for neratinib when compared to what was expected based on patients reconsented, which was 5.1 percent. Therefore, it appears that the missing data has a minimal impact on results.

Lastly, this table shows results from exploratory subgroup analyses based off the primary

analysis with 2 years of follow-up for all the stratification factors. There is no multiplicity adjustment for these analyses, and results should be considered exploratory only.

In summary, the primary efficacy results from ExteNET showed a treatment effect with neratinib with the statistically significant stratified hazard ratio of 0.66. The FDA analyses conducted to address early dropouts and missing data all showed an effect in favor of neratinib. However, the true magnitude of the treatment effect remains uncertain, as the hazard ratio appeared to change with more information. Hazard ratio estimates ranging from 0.68 to 0.73 were observed. Thank you.

Next, Dr. Amanda Walker will continue the presentation with the safety results.

FDA Presentation - Amanda Walker

DR: WALKER: Thanks, Joyce.

Good morning. My name is Amanda Walker, and I will describe the key safety findings of this application.

Here is an overview of my discussion points

regarding the safety and tolerability of neratinib in the extended adjuvant setting. First, gastrointestinal toxicities, especially diarrhea, are common and lead to frequent dose modifications and discontinuations. However, as the applicant has described, prophylactic antidiarrheal regimens may improve its tolerability.

In general, the toxicities of neratinib are non-serious and reversible upon treatment discontinuation, and importantly there's been no evidence of substantial long-term sequelae from treatment with neratinib in this patient population.

Our review focused on the safety population in the ExteNET trial, which contained approximately 1400 patients treated with neratinib. The treatment-emergent adverse events are summarized in this table. Overall, more patients in the neratinib arm experienced a grade 3 or higher adverse event, and the majority of grade 3 events were due to diarrhea.

Slightly more patients experienced a serious adverse event in the neratinib arm, 7.3 percent

compared to 6 percent in the placebo arm. Of note, all but two SAEs in the neratinib arm were reversible, both of which were unlikely related to study drug.

There were a total of 3 fatal treatment emergent adverse events recorded in this study, 2 patients in the neratinib arm and 1 patient in the placebo arm. No deaths occurred within 28 days of study drug, and all deaths were attributed to underlying malignancy; again, likely unrelated to neratinib treatment.

The dose modifications and treatment discontinuations are summarized in this table. In the neratinib arm, over half of the patients required a dose interruption and 37 percent required at least one dose reduction. Twenty-eight percent of patients discontinued treatment with neratinib due to an adverse event, and an additional 8 percent of patients in the neratinib arm discontinued treatment due to subject request, in total representing 36 percent of patients.

Since diarrhea is the most frequent toxicity

associated with neratinib, I would like to highlight the NCI-CTCAE definitions of grade 1 through 4 diarrhea. Please note that grade 3 diarrhea indicates either an increase of 7 or more stools per day over baseline, incontinence, hospitalization, or diarrhea that limits self-care activities of daily living, and grade 4 diarrhea is life-threatening or requires urgent intervention.

In study 6201, referred to by the applicant as CONTROL, it's an ongoing single-arm phase 2 study investigating the incidence and severity of diarrhea when neratinib is administered with intensive antidiarrheal prophylaxis during the first 2 months of treatment. As the applicant described, the protocol has undergone a number of amendments, which has led to changes in the treatment regimens being studied, including the addition of anti-inflammatory, budesonide, and a bile-acid sequestrant, colestipol.

As of the March 22, 2017, safety cutoff date, the median duration of treatment with neratinib was 10.6 months for the loperamide cohort, 5.1 months for the loperamide plus budesonide cohort, and 1.7 months

for the loperamide plus colestipol cohort.

During my presentation, I will use the loperamide cohort as a comparator, since we're interested in the frequency of adverse events and actions taken over the entire 12-month treatment course. The loperamide cohort has the longest follow-up with the median duration of treatment with neratinib of 10.6 months.

A comparison of common adverse reactions in the neratinib arm of ExteNET and the loperamide cohort of study 6201 is shown in this table. As you can see, from the first row, these results suggest that loperamide prophylaxis decreases the incidence and severity of diarrhea in patients receiving neratinib.

The overall incidence of diarrhea was reduced to 77 percent with loperamide prophylaxis from 95 percent without, and the rate of grade 3 diarrhea was reduced to 31 percent in study 6201, from 40 percent in ExteNET. However, more patients in study 6201 experienced nausea, constipation, and fatigue as highlighted in this table.

The results from study 6201 suggests that loperamide prophylaxis may lead to fewer dose modifications; however, discontinuation rates appear similar with nearly a fifth of patients discontinuing neratinib due to diarrhea in both studies. Hospitalizations secondary to diarrhea were also similar with and without antidiarrheal prophylaxis.

As shown here, the overall rates of discontinuation due to any adverse event was actually higher in the loperamide cohort compared to patients in the ExteNET study with 37 percent of patients discontinuing treatment with neratinib due to adverse event despite antidiarrheal prophylaxis with loperamide.

To summarize the safety data, GI toxicities, especially diarrhea, are common with neratinib treatment, which lead to frequent dose modifications and discontinuations. Prophylactic antidiarrheal regimens may improve the tolerability of neratinib, and we await the results of ongoing study 6201 to characterize the toxicity profile of neratinib in the setting of combination antidiarrheal regimens.

Most toxicities of neratinib are non-serious and reversible upon treatment discontinuation, and importantly there has been no evidence of substantial long-term sequelae from treatment with neratinib in this patient population.

In summary, the applicant conducted a randomized, double-blind study of 1 year of neratinib versus placebo in women with HER2-positive breast cancer after adjuvant treatment with trastuzumab. The primary analysis at 2 years showed an approximate 2.3 percent improvement in invasive disease-free survival with neratinib treatment; 94.2 percent on the neratinib arm versus 91.9 percent on the placebo arm.

In order to address uncertainty in the efficacy results due to unplanned adaptations of the clinical trial, imbalance of early dropouts, and incomplete extended follow-up data, we performed a number of exploratory studies, including sensitivity and tipping-point analyses. These results demonstrated a consistent trend in favor of neratinib; however, given the degree of missing data,

the true magnitude of benefit does remain uncertain.

In terms of safety, although there were frequent dose modifications and treatment discontinuations in the neratinib arm, mainly due to diarrhea, most toxicities of the drug are non-serious and reversible.

The FDA requests the advice of the advisory committee on the question listed here. Is the risk-benefit profile of neratinib sufficient to support treatment in the proposed indication, that is as a single agent for the extended adjuvant treatment of adult patients with early-stage HER2-positive breast cancer who have received prior adjuvant trastuzumab-based therapy? Thank you.

Clarifying Questions to the Presenters

DR. RINI: Okay, thank you.

We now have about 45 minutes to take questions from the committee to the presenters. If you want to ask a question, just get Lauren or my attention, and we'll write your name down and get to you in sequence. Please remember to state your name for the record before you speak, and direct your

questions to a specific presenter if you can.

DR. NERENSTONE: Yes, Stacy Nerenstone. This application is really very interesting for those of us who treat these patients. My question is, early on -- this is to the study, sponsor. Early on in the study the amendment was made to not allow patients who were node-negative, stage 1, who had a longer than one year since completing the trastuzumab.

I don't see that as being limited in their application, eliminating those patients. Their application is a much broader indication. And I was just wondering their comment about that?

MR. AUERBACH: The ITT population in amendment 13, which was our final amendment, included both the node-negative and node-positive population, and the study hit its primary endpoint for that entire population. So that was the reason for including the entire population in the intended label.

DR. NERENSTONE: And the time to Herceptin completion? In other words, it had been -- the first

amendment said they eliminated it if it had been completed more than one year.

MR. AUERBACH: Correct.

DR. NERENSTONE: Was that also restored?

MR. AUERBACH: Correct. Let's put the slide up. So you'll see in January 2014, when the last amendment to the trial was done, we had outside statistical experts who recommended that we bring the trial back to its original design, which were the April 2009 protocol design. It was brought back to including both node-negative and node-positive, as well as the patients treated less than 1 year and more than 1 year from completion of trastuzumab.

DR. RINI: Okay. Dr. Morrow?

DR. MORROW: Thanks. The sponsor talks a lot about the tolerability and manageability of the diarrhea. I was looking at study 6201, and there's a lot of focus on the loperamide cohort. I know that the other two cohorts are relatively small, but it would be great to have an idea of how those other two cohorts are doing or any data on that and the manageability of the adverse events.

MR. AUERBACH: To clarify the question, are you asking for updated data from that? Okay. To address that, I'd like to bring up Dr. Susan Moran.

DR. MORAN: Susan Moran, Puma Biotechnology. We do have updated data since the time of the briefing document. And I can share with you, these pie charts are the updated from what Dr. Rugo showed, so it's comparing the ExteNET study with the three cohorts: the loperamide cohort, which you've already seen; the budesonide cohort, which you've seen; and then the updated data from the cohort of patients where they're receiving colestipol and loperamide both for 1 month.

What we've seen with each cohort is that it appears that these additional agents are decreasing the incidence of severe diarrhea and increasing the proportion of patients with no diarrhea or with grade 1 diarrhea at worst.

DR. RIELY: What's the approximate median duration of therapy for the 3 groups?

DR. MORAN: At the time of this cutoff, the loperamide and the budesonide, that's the same cutoff

I believe that we showed earlier. But in the colestipol, it's a little over 2 months.

I just wanted to show -- if you can go back to that, the over time. We've just done an analysis looking at the area under the curve. This shows the cohorts. It shows ExteNET in blue, the CONTROL study loperamide arm in green, and the budesonide plus loperamide in red. And the Y-axis is the average CTCAE grade, and then of course the X-axis is over time.

This also shows that with the ExteNET study without loperamide prophylaxis, we saw the highest grade diarrhea in the first month, and then it decreased over time. And we're seeing with each cohort in the CONTROL study a decrease in the incidence of severe diarrhea in the first month, and then a decrease in subsequent months. Even though we do see discontinuations in the first month, we see that if a patient can tolerate neratinib through the first month, that the tolerability is much improved over the ensuing months.

DR. RINI: I have just a quick follow-up on

the diarrhea. Clearly, that's the major risk of the drug. You present data about duration of diarrhea in the presentation in the document. I'm wondering how exactly you captured that. I think it's actually critically important and something that most studies don't do.

I'd rather have one day of grade 3 diarrhea, than 100 days of grade 2, so I'm wondering exactly how that was captured, how you derived those days of specific grades.

DR. MORAN: If we can have the slide from Dr. Rugo's presentation showing the duration, I believe was in there. It comes from the adverse event data, so the start and stop date of the adverse event. We do ask investigators that if a patient has intermittent diarrhea, that if there's more than 3 days in-between the diarrhea, that they record individual episodes of diarrhea, start and stop date.

DR. RINI: Okay. Dr. Cole you're next. Thanks.

DR. COLE: Thank you. I've got a couple of questions. I agree that the early dropouts is an

issue and a concern, that potentially higher risk -- patients at higher risk for an iDFS event might have dropped out early and more often on the neratinib arm and that could cause a bias.

I was wondering if we have any kind of data or a comparison of those who dropped out early on neratinib versus other patients in terms of prognostic factors.

MR. AUERBACH: Could we bring up the slide? In this slide, you will see the prognostic factors in terms of the patients who dropped out early versus those who stayed on for longer. As you can see, the prognostic factors do not suggest that these were patients with prognostic factors that were higher risk than those who stayed on, so it would not suggest that these were higher risk patients.

DR. COLE: How about tumor size, stage, information of age, things that might be related to an outcome other than dose factors?

MR. AUERBACH: We don't have that data, but we can get that for you.

DR. COLE: Thank you. I had a second

question if I might ask the chair. The second question involves the adaptations, and I agree with the FDA's suggestion that type 1 error rates aren't going to be affected by that. But possibly the generalizability of the trial results might be somewhat affected by a changing study population in relation to the overall target population for the proposed indication. And I was wondering if there was any analysis done of how well the study population's actually going to mimic a target population for the proposed indication?

MR. AUERBACH: The study population in ExteNET is very comparable to the other studies that have been done in adjuvant early-stage HER2-positive breast cancer. That includes the HERA study, the BCIRG study, and other studies as well. They're in line.

DR. COLE: Well, I would note that the HERA study has a lower rate of patients with positive nodes 1 to 3, so there's one potential difference at least.

MR. AUERBACH: Do we have a slide on this? I

thought we -- we can get to that data for you. We've done an analysis of this. And if you look across the spectrum -- and that would include the BCIRG study, the joint analysis, HERA -- it's basically right in the middle.

DR. RINI: Thank you. Spears you're next.

MS. SPEARS: Thank you for your presentation. This is on the same thing about the study population. When you made that change to include the higher risk patients, how many patients had already been enrolled over that course when you made that change?

Then looking at the subgroup analysis, it does look like that lower risk group has a very wide confidence interval and doesn't benefit as much and shifts to the right. So what is your justification of actually leaving that group in? I think that's what we're struggling with.

I'm a patient representative, that risk-benefit thing comes into play. Whether you're a stage 1 versus stage 3, your risk of recurrence is very different.

MR. AUERBACH: To answer the first question

let me bring up Dr. Bin Yao.

DR. YAO: My name is Bin Yao. I'm the head of biometrics group at Puma Biotechnology. You asked the question, how many patients we already had at the time of amendment 3 when we excluded low risk patients. At the time, we had 56 percent patients enrolled.

DR. RINI: Dr. Seidman?

DR. SEIDMAN: Andrew Seidman from Memorial. With respect to the potential for antidiarrheal management to lead to fewer dose reductions, delays, interruptions, and discontinuations, can you comment on any analysis of relative dose intensity and efficacy from ExteNET? Has there been an analysis that might lead one to believe that greater drug delivery could possibly lead to greater efficacy?

MR. AUERBACH: To answer that question, I would like to bring up Dr. Susan Moran.

DR. MORAN: Susan Moran, Puma Biotechnology. Are you asking about the efficacy in patients, or you're asking about the dose intensity?

DR. SEIDMAN: Is there a relationship between

disease-free survival, based on relative dose intensity, who received neratinib in the ExteNET trial? Do the patients who got --

DR. MORAN: I can just show you quickly the relative dose intensity in the neratinib study, in the ExteNET study.

This is just looking at average dose intensity over time where about 60 percent received an average dose of 240 milligrams a day. As we saw, about 30 percent of patients had a dose reduction primarily down to the 200-milligram per day dose; so a small dose reduction just a 40-milligram dose reduction. Less than 5 percent of patients had a dose reduction down below 160 milligrams.

I'll let you speak to the efficacy.

MR. AUERBACH: Dr. Seidman you had asked whether or not we had any data showing that dose intensity affected efficacy. Looking at the ExteNET trial -- to explain these Kaplan-Meier curves, group 1 represents the patients who had a tolerability issue with neratinib and specifically those who had any type of a dose hold or a dose

reduction. Group 2 are the patients who had no dose hold and no dose reduction. Group 3 are the placebo patients.

As you can see on the Kaplan-Meier curve, comparing the patients who had a dose hold or dose reduction resulted in a hazard ratio of 0.72. Looking at the patients who had no dose hold and dose reduction, hence, received a higher dose; the hazard ratio was 0.57.

DR. RINI: Okay. Dr. Burstein?

DR. BURSTEIN: I had a couple questions. First, I wanted to follow-up on Patty's question just to make sure I understood. The number of patients in this analysis who had stage 1 breast cancers would be extraordinarily low; is that correct? Like fewer than 100? It looks like the protocol was amended in 2010, within a year of activation.

Is that correct from the FDA point of view, or the applicant's point of view?

MR. AUERBACH: Can we bring up a slide on that please?

DR. BURSTEIN: You said fewer than

60 patients went on before the amendment; is that right? Fifty-six, so a small number of patients. Percent. Excuse me.

MR. AUERBACH: Here you go, Hal, yes.

DR. BURSTEIN: Do we know the number of stage 1's? I guess was the question.

MR. AUERBACH: T-1 was 899 patients.

DR. BURSTEIN: But that's not the nodal -- that's not the stage right? So that doesn't factor in the nodal --

MR. AUERBACH: Do we have node -- you would need node-negative, node-positive?

DR. BURSTEIN: Yes.

Dr. AUERBACH: Node-negative was --

DR. BURSTEIN: The T-1 node-negative is what the question is.

Dr. AUERBACH: Do we have T-1 node-negative? If not, we can get it.

DR. BURSTEIN: Okay. The second question I had is more for FDA. The company seems to have undergone a heroic effort to retrieve a lot of the data having stopped, and then they've reconsented

75 percent of the patients, which is really quite remarkable under the circumstances. But there's still 25 percent of the patients who are missing.

As I understand the imputation model, it assumes an average risk and what it would take, but do we know that those 25 percent, what they look like in comparison to the other 75 percent in terms of toxicity they might have experienced or other risk factors or demographics? The expectation would be that those not reconsenting might look different from those who did reconsent.

Dr. AUERBACH: Yes. We've actually done that analysis. Can I bring up Dr. Bin Yao to address that?

DR. YAO: Bin Yao, Puma Biotechnology. Slide on. This is the 25 percent of patients who we didn't reconsent. Just to walk you through the table, you see the neratinib is in the first column and placebo the second column. We summarized the treatment discontinuation due to AE. You can see that 36.5 percent discontinued due to AE, and they didn't reconsent back, and then 7.9 percent in the placebo.

More importantly, to address your question on the iDFS, 40 events occurred in these patients who didn't reconsent in the neratinib arm, and 60 events in the placebo arm. When we did the analysis based on the data -- remember these patients didn't reconsent, so we only had their 2-year data. So when we look at their 2-year data, we asked the question what was the effect of these patients who didn't give us additional data who had had a ratio of 0.62?

So very similar with the ITT population that we have shown earlier.

DR. BURSTEIN: If I understand this correctly, the hazard ratio is very similar, but perhaps a riskier group not reconsented with a higher absolute risk of recurrence.

DR. AMIRI-KORDESTANI: I think you're asking about the prognostic factors, and we looked at that. Actually, we don't have a backup slide regarding that, but they were similar.

DR. BURSTEIN: They were similar.

DR. YAO: Yes.

DR. BURSTEIN: Then a question for the

sponsor. The data for ER-negative breast cancers look like there's not a strong signal of activity. This, as the clinicians know, is different from what's been seen in other studies of anti HER2-based therapy where there seems to be benefit across the board. And I'm wondering if there are clinical data to suggest why there might a signal in one hormone receptor subset versus another?

MR. AUERBACH: Can we bring up the Kaplan-Meier curves for HR-positive versus HR-negative, please? HR-positive versus HR-negative. Kaplan-Meier curves, please.

In the Kaplan-Meier curves, Hal, as you point out, there is a different signal seen in the hormone receptor-positive and the hormone receptor-negative patients. Let me start with the hormone receptor-negative patients.

You'll notice that during the treatment period between months 0 and 12, there is a benefit seen for neratinib, and the curves are separated at 12 months. When they come off of the drug is when we see the curves come back together.

You'll remember that a very similar signal -- similar but different -- was seen in the 2-year HERA study, where the HR-negative curve separated while they were on Herceptin and then later came back together. This may be signaling that we need to keep constant suppression on HER2 in these HR-negative patients.

We're actually looking at doing additional follow-up studies where we're looking at giving neratinib for a longer period of time, similar to what's done with endocrine agents, to see whether or not that will bear out in clinical trials.

We do know from the metastatic setting and in the neoadjuvant setting, that the totality of the data suggests that neratinib is indeed active in HR-negative disease.

In terms of the hormone receptor-positive, as you seen on the slide on the Kaplan-Meier curve on the left, we do see a benefit after 12 months, and that benefit is sustained and improved at month 24. This is likely due to the dual blocking of the ER HER2 crosstalk. And as you know, in the hormone

receptor-positive population in the ExteNET trial, both groups of patients are on concomitant endocrine therapy, so the study is actually neratinib plus endocrine against placebo plus endocrine.

The dual blocking of the crosstalk -- if we can bring up that slide please -- to discuss this preclinical mechanism, I would like to bring up Dr. Jose Baselga please.

DR. BASELGA: Jose Baselga from Memorial Sloan Kettering. I think there are two hypotheses here. One is that neratinib could have activity that on its own on ER-positive disease, which we have shown in multiple studies. So that's is one possibility.

The other one of course is that multiple laboratories have shown the presence of crosstalk between ER and HER2, so talking to other labs of Carlos Arteaga, and many others. We have data on our own lab that we show.

So we have published extensively, like many other groups, that whenever you block HER2, or you block PI3-kinase, or you block some of these class 1

tyrosine kinase receptors, you have a feedback response that ER transcription goes up very substantially.

Here you have on the right data on cell lines showing that you increase ER transcription, and you increase ER chromatin remodeling, and ER binding to transcription sites in ER-dependent genes. So I think this could be at play. And if we go into pre-clinical work -- and this is also work from our lab, but many other labs have to produce that -- when you block ER and you block HER2, you have preferential effects.

So I think the two things could be at play, but there is clearly a crosstalk between HER2 and ER.

DR. BURSTEIN: I'm sorry, one more question. As Dr. O'Shaughnessy alluded to since 2005-2006, the standard of care for treatment of the U.S. has been either anthracycline and taxane-based chemotherapy plus trastuzumab or multidrug taxane-based regimen plus trastuzumab given concurrently with chemotherapy. In most respects, patients are treated with an aromatase inhibitor as their preferred

adjuvant treatment, and there are multiple FDA indications for AI-based therapy.

As I look at the demographics, it looks like about a third of the patients would have sequential chemotherapy trastuzumab. About half the patients received presumably tamoxifen only, not an AI. About a third of the patients would have received non-anthracycline, taxane-based chemotherapy. And I'm just wondering how much that prior therapy might have affected risk, and therefore benefit, of the drug in this study.

MR. AUERBACH: Can you clarify the question please?

DR. BURSTEIN: I guess the question is, do you think that the treatment received by the patients, the non-neratinib treatment, was sufficiently standard that we've given them optimal care such that the magnitude of the benefit is something that would still be realistically achieved in contemporary practice, or whether it was somewhat suboptimal, which might have made the intervention look a little more robust than it was otherwise?

MR. AUERBACH: We've looked at the treatments with the endocrine in terms of what dosages they received and percentages, and it didn't appear to have any impact on the activity of neratinib.

DR. BURSTEIN: Oh --

MR. AUERBACH: Can I bring up Dr. Joyce O'Shaughnessy on this?

DR. O'SHAUGHNESSY: Joyce O'Shaughnessy, Baylor University Medical Center. As you saw, what the patients got in both arms was similar in terms of the anthracycline, taxane. My read of that, what the patients received, is real world, and most was about half tamoxifen, half aromatase inhibitor.

Now of course, we've moved towards more aromatase inhibitor therapy. I don't think that would make much difference, though, I don't think. And in terms of their prior anthracycline and taxane use, I think that was also quite -- can we bring up the anthracycline and taxane -- they're prior -- here we go. Thank you.

Most of it is anthracycline -- two-thirds anthracycline and taxane, but there is some of the

lower risk patients who just got taxane alone.

I think this is -- things have changed a bit since this time, but I don't think dramatically, so I think this reflects where we are today, pretty close, a little bit of a change. But I don't think it would dramatically affect the outcome.

DR. RINI: All right. Dr. Klepin?

DR. KLEPIN: Yes, thanks. Heidi Klepin from Wake Forest. I have two questions. One is a follow-up on one of Dr. Cole's questions earlier, which relates to subgroups that may be at higher risk particularly for treatment tolerability issues, and that's specifically the older populations.

There were only 12 percent of patients on this study that were 65 and above I think from reading earlier some of the information. So in thinking about extrapolating the efficacy data and the tolerability data to the older patient, it would be helpful, even though the numbers would be small, to hear at least what you have that you could report on --

MR. AUERBACH: Certainly.

DR. KLEPIN: -- is the diarrhea risk similar. Because certainly the tolerability of diarrhea differs in older patients, and is the efficacy signal similar.

MR. AUERBACH: To answer that, I would like to bring up Dr. Susan Moran.

DR. MORAN: Susan Moran, Puma Biotechnology. We've looked at safety stratified by age under 65 and 65 and older, and we did not see a higher incidence of diarrhea or severe diarrhea in the older patients, although we saw that the older patients were more likely to discontinue as a result of diarrhea.

We also did not see a higher risk of severe dehydration or severe renal toxicity, although we did see in the older patients that they were more likely to have these renal adverse events all related to pre-renal volume depletion and all reversible with hydration or study drug interruption.

Then in the CONTROL study, we have looked at this also and seen a very similar pattern. So with the antidiarrheal prophylaxis we do not see an increase in diarrhea or severe diarrhea. We do see

that the patients are more likely to discontinue if they're older, but we don't see an increase in severe dehydration or renal problems.

DR. KLEPIN: Thanks, and I had a second question related to patient reported outcomes and quality of life. There were some measures that were included in the study, and I realize that -- I don't think they were presented --

MR. AUERBACH: Yes.

DR. KLEPIN: -- here today. I didn't know if we could comment on those?

MR. AUERBACH: So to talk about the quality of life, I would like to bring up Dr. David Cella.

DR. CELLA: Good morning. David Cella from Northwestern University Cancer Center. I'm a paid consultant to Puma, and I derive no financial benefit based on the outcome of this meeting.

In the briefing package, you saw a summary of this analysis, and I'm showing this particular one. It's really a representative of virtually all of the other analyses that were done that were planned. This is an exploratory endpoint, so this was the

first-line exploratory endpoint if you will, looking at the trial outcome index of the fact B, which includes 23 questions on physical functioning, functional wellbeing, and breast cancer symptoms.

You'll see that a statistically significant difference at 1 month, which is of a magnitude that we would not consider to be clinically meaningful. It's in the range of 3 to 4 points, and we would want to see a difference of 5 to 6 points to consider it clinically meaningful.

So overall, when patients are asked about their functioning, and about their wellbeing, and about their symptoms, generally we don't see a difference. But embedded within that set of questions, there is a single question about bother with side effects of treatment that's particularly relevant to this conversation.

Can you also get ready QL-72? This shows you the comparison of neratinib to placebo on the ExteNET trial, where on average, the patients receiving neratinib -- I'm going to show you axitinib in a moment -- shows in between a little bit and somewhat

bother with side effects at that first month, and then it kind of levels off after that. And you see the placebo group as a comparison.

When we compare that to published data on the AXIS trial looking at axitinib and sorafenib, we see what you could consider in this one question about side effect bother, what one might call a TKI signature where you get this increase in bother with side effects early on that sort of levels off after that. So it's very comparable in terms of its magnitude, in terms of the patient's experience of bother.

One last thing, because it may be on your minds, is that when we look at the patients who come off the therapy, who discontinue at their request or because of toxicity, those scores average right at the somewhat point. So if they say that they need to come off therapy, they can't tolerate it, their scores average around 2. So you're in that range of a little bit to somewhat across the experience of the range of side effects with neratinib.

DR. RINI: Somebody who has a specific

follow-up question on this point?

DR. AMIRI-KORDESTANI: Actually, can I jump in here? FDA has also looked at the PRO data. We have I believe three backup slides on this. I would like to ask Dr. Amanda Walker to comment on this.

If you bring slide 44.

DR. WALKER: Thanks. So I'll just run through my backup slides on this. As was previously mentioned, the PRO data were collected as exploratory endpoints, and then the FACT-B and the EQ-5D were the instruments that were used.

I just want to mention that the overall scores of each instrument is -- the overall scores are difficult to interpret. They contain a number of global elements that might be unrelated to treatment at all. Especially in an otherwise healthy patient population, it makes the interpretation of the overall score very difficult. And none of the instruments that were used captured diarrhea specifically.

You can go to the next slide. When we looked at the FACT-B, we took a look at the item level

analysis that particularly felt most relevant to us in this patient population, which was physical wellbeing. It asked a number of questions, which are listed here. You can go to the next slide.

When you looked at the combination of the overall score for this particular subset of questions, from the physical wellbeing subsection, you see that there was an average of 2.5 drop in the score at month 1, and then there was a persistent decrease similar to what was previously shown, when you just look at whether or not patients were bothered by their toxicities. When we looked at what was driving this, that was the number 1 thing that stuck out for us, as well as nausea.

So taken together, I think you need to -- there may be an impact in terms of the quality of life in this patient population. I think no one really knows how to really interpret the clinical meaningfulness of these results, but it was important just to consider.

DR. RINI: Okay, Dr. Minasian.

DR. MINASIAN: Along those lines, is this the

time frame where most of the treatment discontinuations occurred, either by patient request or clinician specifically?

DR. WALKER: That's a really good question. This analysis that we are presenting here is mean change from baseline, and only included patients who were receiving neratinib. So we had other data, that patients were given the questionnaires after they had discontinued neratinib. But we were only looking at patients who at the time of the questionnaire were being treated with neratinib.

DR. RINI: Dr. Royce did you have a question as well?

DR. ROYCE: Yes, a different line, but a follow-up to an earlier question in the subgroup a prime since the last trastuzumab.

Looking at your pre-specified subgroup population, greater than one year is actually quite small, and the confidence interval is quite wide. In real world, these would capture a very, very small subset of population today, and the benefit seems to be quite small.

Just a point of clarification though, you are not limiting your application. You're not excluding this group, right?

MR. AUERBACH: Correct. Let me bring up the forest plot. The last two rows you will see is the time from completion of trastuzumab. And you are correct that the hazard ratio for the less than one year is better than the hazard ratio for the more than one year.

Again, this is an exploratory analysis, and these are exploratory subgroups. The trial hit its primary endpoint in the intent-to-treat population, and that is the reason for us filing for approval in the entire intent-to-treat population.

DR. RINI: Thank you. Dr. D'Agostino.

DR. D'AGOSTINO: One of the major concerns that has come up here obviously is the dropout and the change of sample sizes, and I'd just like some clarification to make sure I'm following. We started off with 3,850, and then we end up with 2,840. And that goes through this change of Wyeth to Pfizer, and then the idea of keeping more severe individuals and

so forth.

Is it the 2,840 that the FDA is focused on in terms of their sensitivity analysis? The comments that Dr. Cole was making about these early dropouts and so forth, we're not dismissing them, but we have an explanation that as was given.?

Am I right about the sensitivity analysis? I just want to make sure. I'm looking at your slides 19 and 21, and you're dealing with just the 2,840 individuals. This is the FDA's presentation. Correct?

DR. CHENG: Yes, that's right.

DR. D'AGOSTINO: And just again so that the vocabulary is clear, when we say 75 percent reconsented, what exactly does that mean? Out of the 2,840, what does that 75 percent reconsented mean?

DR. CHENG: They were reconsented to be followed past 2 years. The primary analysis only included data up to 2 years 28 days post-randomization, and then patients could be reconsented after amendment 13 I believe for a further follow-up up to 5 years.

DR. D'AGOSTINO: If you go to your slide 19, and you look at 3 months, am I reading the 3 months correctly, that it's 1288 and 1367? Those are the individuals that were still in the study and didn't have an event from 0 to 3 months?

MR. AUERBACH: In the primary analysis, there was 1,288 neratinib patients available. When we did the reconsenting, we ended up having a number of those early censored patients that we got longer term follow-up on, so we ended up having a higher number of patients at risk. And I believe the FDA's analysis shows that and ours also.

DR. D'AGOSTINO: That's what I'm getting to. It looks like you start off with -- when you go to slide 21, you have the same number of individuals at the start.

Can you go to slide number 12? his is again the FDA's presentation.

MR. AUERBACH: FDA's slide, yes.

DR. D'AGOSTINO: You have the same number, the 1420 in each group, but the 3 months here has more individuals than the 3 months had with the

previous slide 19. How did you get more individuals?

MR. AUERBACH: When Puma did the reconsenting process in amendment 13, a number of the patients who were early censored, so we only had observations on them prior to month 3 previously in the primary analysis, reconsented, and we ended up getting additional follow-up information on them. So because of that, we ended up having -- you'll notice there's more patients at risk in the 0 to 3 month, but also in the 21 to 24 months.

DR. D'AGOSTINO: If you have already 75 percent reconsenting, how did you start off with 2,840?

MR. AUERBACH: 2,840 is the number of patients who enrolled in the study and were administered either neratinib or placebo.

DR. D'AGOSTINO: But what does the 75 percent consented mean? You're not looking at just the 75 percent consented?

MR. AUERBACH: It's the 75 percent of the 2,840.

DR. AMIRI-KORDESTANI: Both analyses are ITT.

DR. D'AGOSTINO: What's that?

DR. AMIRI-KORDESTANI: They are ITT, so they take into account all the ITT.

DR. D'AGOSTINO: You're taking into account all the individuals. Yes, I just want to make sure we're understanding --

(Crosstalk.)

DR. AMIRI-KORDESTANI: It's the number of censored patients are different, correct.

(Crosstalk.)

DR. D'AGOSTINO: -- because some may say the 75 percent reconsented might drop 2,840 --

MR. AUERBACH: No.

DR. D'AGOSTINO: -- to only that 75.

MR. AUERBACH: Right.

DR. D'AGOSTINO: So you're keeping the full group, as long as you have information on them, and you got more individuals --

MR. AUERBACH: Correct.

DR. D'AGOSTINO: -- with the reconsent. Thank you.

MR. AUERBACH: That's correct.

DR. D'AGOSTINO: Yes, I think it's very important because the sensitivity analysis is very striking and one may get -- as I was wondering how these numbers are jumping around, but you explained it. Thank you.

MR. AUERBACH: Sure.

DR. BURSTEIN: So can I clarify, did FDA do an analysis of just the 75 percent for whom 5 years of follow-up was available not including the first 2 years, which would be the whole cohort?

DR. D'AGOSTINO: That was going to be my next question. That's the thing you would have thought naturally was the analysis, and that's why I'm raising my questions and you're following up.

DR. CHENG: Are you asking if we did an analysis only including the 75 percent that are reconsented? We did not do that analysis. The analysis we did was for the full ITT, including 75 percent who had further extended follow-up data.

DR. RINI: There's a comment.

DR. SRIDHARA: This is Dr. Raji Sridhara, the division director of biostatistics. The point is if

you're looking even at those 75 percent reconsented, we did have some of that information in the 2-year data as well already. So you can kind of take out that only 75 percent reconsented. They did have the information up to 2 years, so there would have been --

DR. D'AGOSTINO: I agree with you whole heartedly. I just wanted to make sure there was clarity, so when one was looking at this table and these figures, that they're understanding what --

DR. SRIDHARA: Yes.

DR. D'AGOSTINO: -- we actually have.

DR. SRIDHARA: So what happened was some of them who were dropped out early or who were censored before, either they had events or they came to know that they were still alive and disease-free at 5 years when they reconsented, some of the dropouts that we saw.

So the numbers went up in the 3 months that you see at risk, which were totally dropped out, and there was no information beyond that. Now they had information beyond that 3 months. Either they had

events before 5 years or they were still alive and no event at 5 years. So, that's how the numbers went up in this analysis.

MR. AUERBACH: Dr. D'Agostino, I believe Bin Yao from Puma Biotechnology would like to speak.

DR. YAO: We did look into the 75 percent patients, so I have an analysis that I want to share with you. However, I think the ITT analysis that you have seen earlier is what we had in analysis plan, this is another exploratory analysis.

DR. D'AGOSTINO: Just to clarify, it was the vocabulary sitting on the graph, 75 percent reconsented, which is not really completely correct because it's an ITT-type of analysis. But I think you've clarified it fairly well.

DR. YAO: Right. So here we are looking at 2,117 patients who reconsented. You can see the breakdown by the treatment arm, and we conducted a sensitivity analysis because here with the 2,117 patients we no longer have the randomization to afford comparability between the two treatment arms.

So what we did was we used a methodology

called propensity score method to ensure that we are able to compare these like apples-to-apples and adjusted a baseline imbalances, potential imbalances. As you can see, the estimated iDFS hazard ratio was very similar to when we used all the patients we included in the 5-year data.

DR. RINI: Ms. Spears, do you have a question?

MS. SPEARS: I kind of wanted to come back to the side effects and the safety and the diarrhea in the CONTROL study. It seems like in the CONTROL study for the prophylaxis, you're trading off CTCAEs from diarrhea to other kind of events. So I really like the slide that was shown by Dr. Moran about the CTCAE of the diarrhea side effect over time.

Do you have the total CTCAE side effect profile of the three groups over time? And, is there more effort being made now in these new studies to collect the appropriate pro-data that is really looking at diarrhea and constipation and fatigue that you know are going to be issues with these patients?

MR. AUERBACH: So we do not have those graphs

over time looking at total CTCAE scores. We can try to generate that today, and see if we can get that to you. But we are making a concerted effort to collect this, and Dr. Hope Rugo would like to comment on this.

DR. RUGO: Not that I can provide you with that specific information, but in treating patients with neratinib and using the prophylactic regimens, it is interesting that loperamide has to be modified by the individual to manage the constipation and diarrhea. And just like every treatment that we give our patients, we manage it on an individual risk versus benefit.

So first you had asked earlier about stage 1 disease; you're going to make a risk versus benefit. The same as for a very elderly patient versus a younger patient, we make those decisions with chemotherapy, with hormone therapy, with everything we do in the early stage in a metastatic setting.

In terms of managing the diarrhea, it's really a patient education and a team understanding approach, so that in the patients I've treated on the

CONTROL study, I have zero dropouts. It's an interesting thing that all of these things, just like managing chemotherapy toxicity, that experience is critical and helps our patients.

DR. RINI: Dr. Royce, do you have a follow-up?

DR. ROYCE: Not a follow-up, but it may not be fair to ask the company, but I will ask anyway.

Given that we will be asked to make a recommendation -- and I know it's a secondary endpoint, and most of the approvals for drugs that we'll be making the recommendations have at least some approval in the metastatic setting -- when might you expect an overall survival data?

MR. AUERBACH: The overall survival data will be analyzed when we hit 248 events. We're currently blinded to survival, so we don’t anticipate hitting that number of events any time soon. I would estimate somewhere in the next 2 to 3 years.

DR. RINI Yes, Vali?

DR. PAPADIMITRAKOPOULOU: Okay, so I will go back to the subgroup analysis. I am puzzled why when

all the benefit is seen in the HR-positive group, and it drives the overall benefit, why we're still considering the HR-negative group for this indication?

MR. AUERBACH: The data in the HR-positive group is obviously an exploratory subgroup, and the trial hit it's endpoint for the intent-to-treat population. So that's where we're applying for the approval of, for the entire intent-to-treat population.

DR. PAPADIMITRAKOPOULOU: But you have a hypothesis about HER2 ER crosstalk, and I just heard that you were thinking of more extended exposure of the patients?

MR. AUERBACH: In both HR-positive and HR-negative.

DR. PAPADIMITRAKOPOULOU: That's right.

Okay. The other also speculative question is since you have such a high rate of early dropouts and we have uncertainty about the extended data in the exploratory analysis at 5 years, how do you view the trial data with HERA, for example, trastuzumab, 1

versus 2 years. Originally there was a benefit that disappeared over time, so how do you put this in the context of your data and how certain are we?

MR. AUERBACH: So in terms of the HERA study, I believe Dr. Jose Baselga was involved with that. I would like to bring him with comments. But my preliminary comment would be, one of the things that's interesting about the neratinib study is that we're seeing the benefit in HR-positive disease, and in HR-negative, we're seeing the curve separate and come back together. I don't believe that was seen in the HERA study where they saw a benefit in the HR-positive.

Dr. Jose Baselga, please?

DR. BASELGA: Thanks for calling me to this. I'm not a statistician. I can give you, in HERA, it was continued therapy and very clear that the 2-year initial benefit then was lost, but following patients that had subclinical disease that we tested for longer.

Now, I think that the difference that you're mentioning here -- again, I'm not a

statistician -- is that if you look at the data on the extended follow-up, the 5-year data, although it's supportive and it's not the primary endpoint, it is very supportive of the 2-year data. So, we don't see what was seen in HERA in the ExteNET study.

DR. PAPADIMITRAKOPOULOU: Can I ask you to speculate --

MR. AUERBACH: I would also like to bring up Dr. Joyce O'Shaughnessy to comment on that.

DR. PAPADIMITRAKOPOULOU: Okay.

DR. O'SHAUGHNESSY: Joyce O'Shaughnessy, Baylor. Just two points on the ER-negative first. ER-negative HER2-positive disease is really heterogeneous. When you do expression analysis like with a PAN-50 for example, the ER-negative will go into actually four different buckets of luminol A or luminol B, or HER2 enriched, and basal-like. So we know it’s very, very heterogeneous.

So because it's exploratory, we don't really know whether there are subgroups within that ER-negative that may benefit considerably. We have an analogy here from the CALGB 9344 trial when

adjuvant AC was the standard, and it was plus/minus paclitaxel, and the overall population benefited. It was statistically significant for both disease-free and overall survival. But all of the benefit was seen in the ER-negative. There was nothing in the ER-positive, and there was a lot of uncertainty initially about what to do with that in practice because it was approved for the whole population.

It with subsequent follow-up, that actually went away. And it has turned out that ER-positive disease is so heterogeneous with luminol A and luminol B, that the benefit really accrues to the luminol B, which we figured out over time.

So in the ER-negative population, in my view, there's very likely to be a population that will benefit particularly potentially some of the luminol patients.

With regard to the HERA where it splits and then comes back together again, my read of these curves is that these definitively stay apart, and it's particularly impressive in the ER-positive population because the curves continue to split over

time. It really gets impressive when you look at the centrally confirmed HER2-positive, really gets impressive.

So I believe that's quite real the way that splits apart, and we know that when you block that HER family, we will get signaling through ER, and you'll probably get a more benefit from your endocrine therapy.

DR. RINI: Okay, Dr. Nerenstone did you have a question?

DR. NERENSTONE: I'd actually like to ask the FDA, because it's still really bothers me that when you look at the patients who were put on study greater than one year after HER2 was completed, that when you look at their benefit, even in the 5-year it's actually one, which means the implication is there really is no benefit.

When we're looking at this broad application, you're talking about thousands of women who may be eligible in theory, but the likelihood of benefit is very small. And I understand about subgroup analysis, but what bothers me is that the sponsor

themselves said early on, gee, we need to enrich this population because this is a population which is not likely to benefit, and then changes their mind at the very end after it's been changed and accrual has been completed.

So explain to me statistically why that is still pristine at the end. And I understand about subgroup analysis and they're exploratory, but that really bothers me when the approval is so broad. So basically anybody who's finished the Herceptin treatment 5 years ago who was without evidence of disease could say, okay, I want this drug, and I'm not sure they would have any benefit from it.

MR. AUERBACH: So just a point of clarification for the comments, it was actually up to 2 years enrollment of the trial. So a patient who was 5 years would not have been applicable.

DR. NERENSTONE: So you probably need to make that change also --

MR. AUERBACH: Okay.

DR. NERENSTONE: -- in your application --

MR. AUERBACH: I appreciate that.

DR. NERENSTONE: -- at least that.

DR. SINGH: Harpreet Singh. I can comment from a clinical perspective, and Dr. Cheng can comment from a statistical perspective.

From a clinical perspective, you note that we are all aware of the issues with subgroup analyses, and if the indication were to be granted broadly, we believe that this would be a practice of medicine issue that discerning physicians would look at this data and make individualized patient decisions based upon the patient's characteristics, ability to tolerate side effects, and potential benefit or lack thereof.

I'll let Dr. Cheng comment as far as how statistically pristine these analyses may be.

DR. CHENG: Hi. I don't have any additional comments other than what you've already brought up, which is that these analyses are considered exploratory from a statistical point of view.

DR. AMIRI-KORDESTANI: I want to add a clinical -- actually as a clinician I think the doctors are going to have this conversation right

after their patient finishes trastuzumab. So I think in practice, it's going to be given following completion of trastuzumab therapy, even though the trial was not conducted that way.

DR. MINASIAN: But to Dr. Nerenstone's point, there are patients that have completed trastuzumab for quite some time ago. And if the eligibility originally was less than 2 years of completion, that should be part of the indication.

DR. RINI: We're running short on time. Maybe just one more, Ms. Preusse.

DR. SRIDHARA: Can I just add one --

DR. RINI: Sure. Sorry.

DR. SRIDHARA: -- more point? This is again Raji Sridhara from FDA. So the subgroup analysis is always -- you do it as exploratory, and it is hypothesis generating at best. If you look at this one particularly, it's a very small sample size and very few events have occurred. So as you follow up further, more events are -- one way or the other, this could change very well. And the confidence interval is so wide, there is so much of uncertainty,

anything to talk about that particular subgroup.

So I think other than saying the ITT, the overall population did show a difference there, I don't think we can comment on the subgroups.

DR. RINI: Do you have one more?

MS. PREUSSE: Thank you. Courtney Preusse, patient representative, also at the Fred Hutch. Expanding upon Dr. Burstein's original comment regarding current standard of care, I am trying to put myself in the shoes of a patient who would be eligible for this treatment. And looking at what is currently available, I am struggling greatly with trying to understand the added benefit of this new treatment drug as compared to, for example, lapatinib and trastuzumab.

For example, on page 4 of one of the slides where the ALTTO trial is mentioned, there's a nominal improvement of about 2 percent, and then further into the drug company's presentation the improvement in disease-free survival in the ITT population is 2 percent.

So in that regard they seem comparable, but

then looking at the AEs associated with these HER2 agents, the grade 2 events associated with neratinib are 54 events as compared to only 24 events in lapatinib.

So from a layperson's perspective, I'm getting the same overall disease-free benefit with the either drug but having more side effects on neratinib. So I'm just really trying to wrap my head around this, and I'm hoping somebody can point out what I'm missing.

MR. AUERBACH: To answer this question, I would like to bring up Dr. Jose Baselga.

DR. BASELGA: Thank you very much. Jose Baselga from Memorial Sloan Kettering. So let me share the way I see this. There are two questions that you're asking. One question is where would this fit in our current practice? And then the second question is, what about this versus ALTTO?

I can talk about ALTTO because I was one of the co-investigators, and I was also on the steering committee, so I was there as well.

So I think the first question, where does

that fit? I think the data that we have seen shows that there is a relative risk reduction of 34 percent to what is currently available for patients with early disease. I think this speaks to the practice of medicine, and this will based on multiple decisions. So it will be based on the perceived risk of recurrence that the given patient may have, it may be based on patient preferences, and it may be based on all of the criteria.

But the question is would you like rather to have this option available to your patients, yes or no? And to this I will answer, yes. That has been what we've been fighting all these years, right? And that's why we're all here, because we want to have this option available to our patients. And a 34 percent relative risk reduction to me sounds like a lot, and I would go a long way to get this done.

ALTTO, there's no question in my mind, and in anybody's mind, that ALTTO, there was something there. There was something there, but it did not meet its primary endpoint, and there are multiple reasons why that happened, and many of them are

speculative.

Lapatinib is less potent than neratinib, and I think that is the reason that it's unquestionable. It is much more potent, and I think that maybe carried the day, but it could be other things. So if lapatinib had been a positive study, we would have lapatinib available, but we don't. So I think that's the nature of clinical research, and that's the data of -- and that's the business of going by data. That's my view, thank you.

DR. RINI: So we're going to take a break now. There may be some more opportunity for discussion after the open public hearing. We will resume at 10:40 promptly. Remember, for the committee members, there should be no discussion of the application at any time during the break amongst yourselves or with anybody else.

For the committee members who are staying for the P.M. session, if you have a lunch form, you can take it to the kiosk now, and we'll see everyone at 10:40.

(Whereupon, at 10:27 a.m., a recess was

taken.)

Open Public Hearing

DR. RINI: We're going to start the open public hearing session.

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

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

Likewise, FDA encourages you at the beginning of your statement to advise the committee

if you do not have any such financial relationships. If you chose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

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

One our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please only speak when recognized by the chairperson.

Thank you for your cooperation, and I'll ask speaker number 1 to step up to the podium, introduce herself, and state your name and the organization you are representing for the record.

DR. FOX-RAWLINGS: Thank you for the opportunity to speak today. My name is Dr. Stephanie Fox-Rawlings. I am a senior fellow at the National Center for Health Research. Our research center analyzes scientific and medical data to provide objective health information to patients, providers, and policymakers. We do not accept funding from drug and device companies, so I have no conflicts of interest.

The pivotal study that is the basis of today's review only demonstrates a small improvement in the primary efficacy endpoint. After 2 years, about 2.3 percent more patients were without invasive disease if they took the drug compared to placebo.

This difference was statistically significant likely because of the large number of patients in the study. However, such a small difference could be specific to this particular sample of patients and trial and might not be generalizable for all women with early-stage breast cancer. It is impossible to say, since after

2 years over 90 percent of patients were free of invasive disease whether they received drug or placebo.

Patients followed for 5 years had a similar result. About 2.5 were more likely to be cancer free while almost 90 percent of the patients taking the placebo were also cancer free. There's no data yet on the overall survival, so the results aren't compelling.

This small difference should be considered in the context of adverse events that are typical of cancer drugs. Diarrhea, nausea, vomiting, and fatigue were common; however, some were categorized as serious events. Adverse events were so unpleasant they caused 28 percent of patients taking the drug to drop out of the study, compared to just 5 percent of patients taking placebo.

The sponsor also presented data from an ongoing open label, single-arm study aimed to reduce adverse events due to diarrhea with prophylactic treatment; however, there was still a high occurrence of diarrhea, and the treatment of

diarrhea caused a different set of adverse events.

Patients should not be exposed to adverse events if the drug isn't proven to provide real improvement. The 2.3 percent difference between 91.9 percent and 94.2 percent is not impressive, and with only one pivotal study, there's no way to know if the result would be replicated in a second study.

A recent study published in JAMA Internal Medicine found that when FDA approved cancer drugs based on a surrogate endpoint, such as cancer free survival, later studies have not found a benefit in overall survival. Yet, these drugs cost an average of $100,000, often more, and can harm quality of life.

We've seen the benefit compared to placebo is similar to that of a previously approved drug. This does not mean it should be approved. Patients do not benefit from more new drugs on the market unless the new drugs are more likely to have benefits that outweigh the risk.

The FDA should be sure that new treatments

provide a real benefit to patients before they are approved. We recommend that the FDA not approve the drug for breast cancer unless a clear benefit can be replicated or benefit an overall survival as demonstrated. Thank you.

DR. RINI: Thank you. Speaker number 2?

MS. JEWETT: Hi. My name is Kimberly Jewett, and I would like to disclose that I'm a paid consultant for Puma. I was diagnosed at the young age of 31 with breast cancer. My daughter was 6 years old and my son was 4.

As I navigated the treatment journey suggested by my healthcare team, I was told to have a radicle mastectomy, chemo, and hormone therapy. I followed every single recommendation hoping and pray that I would have more time to raise my young children. The thought never left my mind wondering what life would be like if mommy was no longer alive to guide them through life.

The fear, the anxiety, the loss of control and uncertainty that a cancer diagnosis brings a patient and their family is overwhelming. As I

tried my best to resume my new normal following treatment, all of these emotions escalated, and at times they had me in my oncologist's office crying with feelings of despair worried that the cancer was growing somewhere in my body. Had I done all that I can to reduce my risk of recurrence?

Three and a half years later the disease came back, I was 35 years old. My daughter was 10 and my son was 8. I will never forget coming home to see my kids after I heard the news, you have cancer. My daughter looked at me and asked if I was going to die. I had no idea how to answer that question because I did not know the answer at the time, but what I did say is that I would do everything possible, that I would fight this disease, and that the man above had the final say and our prayers to God would give us the hope that we needed to navigate this treatment phase.

While I am grateful and blessed to be standing here today sharing my journey with you, I have lost so many friends to this horrific disease, one in particular who was also young who had hoped

to take neratinib before her cancer took her life way too soon. I think about my dear friend each day. I often wonder if neratinib was available as an option for her to take, would she still be with us.

How many other countless women have reduced their risk of recurrence giving them a sense of control while minimizing the fear and anxiety they have knowing they are doing everything they can possible to reduce that risk, combined with the thought of quality of life that is so important for patients to make when making treatment decisions?

It is my sincere request to advocate that the FDA should strongly consider approving neratinib for patients and their families that need options. Patients deserve their fighting chance to do everything they possibly can to reduce this risk of recurrence and that they hopefully never have to deal with this horrific disease another time.

I am the voice of many patients, women that are fighting, surviving, and thriving every single day of their life. And let us not forget the women

who unfortunately lost their lives way too soon and would have done anything to have a chance for neratinib.

DR. RINI: Thank you. Speaker number 3?

MS. GERARD: I would like to disclose that Puma paid for my travel expenses. My name is Fern Gerard. In 2008 while breast feeding my son, I discovered a lump in my breast. I had HER2-positive cancer. I didn't want to do chemo, as I was afraid it would destroy my immune system. However, my family convinced me to do a double mastectomy.

At the end of 2009, a scan showed cancer in my lungs and bones. My first experience with chemo was with Taxotere and trastuzumab. I lost my hair, experienced nausea, and felt terrible.

In May 2011, when the cancer progressed, I was switched to the TDM1 arm of the trial I was on. TDM1 worked well for me; however, it did not cross the blood-brain barrier, and I needed brain radiation for numerous mets. Over the past eight years, I have tried multiple chemotherapies,

including pertuzumab and trastuzumab.

The cancer in my lungs caused fluid to accumulate, and my doctor wanted me to get a lung catheter. I was fearful that it meant accepting inevitable death. I knew that my friends who had done this had not survived long enough to have it removed. Instead I did 5 thoracentesis procedures.

In August 2016, I needed whole brain radiation for numerous brain mets. I bled from my ears, and my head hurt painfully. Prior to starting the chemo Navelbine, I had been experiencing cachexia. This was now replaced with generalized edema.

Next we tried Halaven. This chemo made me look like I'd been in a fight. I was on oxygen 24/7, I could barely walk, my belly was swollen with ascites, which required paracentesis. The cancer was in my liver and lungs. It seemed that I'd run out of options, as my condition made me ineligible for any clinical trials.

In December 2016, my doctor wanted to put me on hospice. Fortunately, once I started neratinib,

that was no longer necessary. My CEA markers dropped from 964 to 63 over a 3-month period; all my other markers returned to the normal range.

I expected to experience diarrhea, but for me it does not appear to be a side effect. I can breathe without oxygen, I can hike, my hair is growing back, I'm living life again, I'm here for my children, and I'm so happy to be here, and everyone is amazed.

I want everyone to know that you'll never truly understand something until it happens to you. We need more options. I have friends dying. This drug needs to be approved. I would not be here today if it was not for this drug. Thank you.

DR. RINI: Thank you. Speaker number 4?

DR. BARRY: Good morning. First, I would like to disclose that my travel expenses were paid by Puma.

Good morning. My name is Michelle Barry. I recognize the powerful opportunity you have here to afford a critical sense of hope to cancer patients. Thank you for considering our humble yet insightful

perspectives as patients in your decision-making process. Your recommendation to approve neratinib would give patients another option, which can equate to strength, improve quality of life, and ultimately hope for HER2-positive cancer patients, as my story can illustrate.

At the age of 41, I was diagnosed with hormone receptive HER2-positive invasive ductal carcinoma. I was not surprised to find a lump being a third generation survivor; however, to hear the words "You have cancer," is still universally shocking.

Upon receiving my initial biopsy results, I was relieved to hear I had a rather common grade 2 hormone receptive tumor. To then hear based on subsequent surgical pathology that my tumor was in fact grade 3 and HER2-positive was a devastating blow to my optimism. One frantic Google search later, I knew I was facing a much more aggressive cancer, and my anxiety grew exponentially.

I was encouraged by my neighbor, a fellow HER2-positive survivor herself, to be grateful for

the one drug that was available at the time to treat early-stage HER2 cancer. I quickly made the connection between drugs and hope.

My oncologist alerted me to a clinical trial for which I might qualify to receive an additional drug, and I was overjoyed at the prospect that I could employ two weapons of cancer destruction against any elusive rogue HER2 cells. I felt embolden by my choice to join the trial only to suffer eventual despair upon learning I did not qualify.

As chemo progressed, life and my sense if hope hinged on the ever decreasing values on my labs. When my forth infusion had to be held for low platelets, I was racked with fear that I was being left vulnerable to an increased risk of recurrence. I was still hanging my hopes on the drugs.

Could getting that additional drug have instilled me with greater courage or optimism while staring recurrence risk in the face? Absolutely. And for this exact reason, I'm here to advocate on

behalf of thousands who are hopeful for your recommendation and support of neratinib.

The trial results are particularly impressive in hormone-receptive patients like me, making it an enchanting possibility. I have since had the opportunity to make choices and changes regarding my hormone therapy, weighing benefits versus side effects all along. I've been empowered by each opportunity to make decisions, albeit difficult ones, regarding what treatment is best suited for me based on my unique tolerance for risks, side effects, and fear of recurrence.

Almost five years into this journey, I'm at peace with the decisions I've made and grateful for the treatment I've received. But would I still jump at the chance to take another drug? Absolutely.

It's my hope that more drugs such as neratinib will be approved so patients going forth can have more choices, more control, less fear, and improved quality of life.

I'm here to speak on behalf of everyone,

which statistically and sadly can include my younger sister or, God forbid, my daughter, who'll have to decide what comes next after hearing the dreadful words "You have cancer."

Until there's a vaccine or a cure, my family and patients everywhere everyday are counting on more drugs such as neratinib to be approved, which may deliver a crucial dose of hope. Thank you.

DR. RINI: Thank you. Speaker number 5?

MS. DAVIS: Hi. My name is Debbie Davis, and I would like to disclose that Puma Biotechnology paid for my trip to come here. I've been on neratinib since March of 2016 through the Compassionate Access Program. I'm a 24-year breast cancer survivor, and I have 17 years at stage 4.

My original diagnosis was stage 2 ER-positive breast cancer. My cancer became metastatic to the bone in 2000, and that's when it was discovered that my cancer was HER2-positive ER/PR-negative.

I've been treated at Siteman Cancer Center in St. Louis Missouri by Dr. Ron Bose and

previously by Dr. Matthew Ellis. A spot was discovered on my liver in 2007, and since then I've been on 15 different lines of chemotherapy with a variety of different side effects. I've lost my hair 4 times in 24 years, and I love the fact that I can keep my hair on neratinib.

The only side effect I've had is the diarrhea, and that has been controlled by loperamide and has never changed the way I've lived my life. I've never had nausea or stomach cramps, and I work full-time, go to a work out class 2 times a week, a very active social life, and I don't feel like I look or feel like I have cancer.

I'm dealing with one aging parent. And my only child that I had after I was originally diagnosed back in 1993 is going to college out of state, and thanks to neratinib, I've had 14 more months with him of wonderful memories and moments that I cherish. I love to quote the saying, "I'm way too busy to have cancer," and neratinib certainly allows me to live my life to the fullest.

I receive CT scans every 2 months, and they

have shown stable liver lesions and no new metastasis. The main liver lesion has been as large as 8 by 8 centimeters and is now stable at 1.4 centimeters by 2.2 on neratinib. Really since 2008, this is the only chemotherapy drug I've been on that's lasted more than a year without progression, and I've been on neratinib now for 14 months.

In closing, I'm here today advocating that neratinib be approved so that other breast cancer survivors and patients can have the same options and hope available to them that I've had. We should all have this choice, and neratinib has allowed me to live a wonderful side-effect free life.

DR. RINI: Thank you. Speaker number 6?

MS. LURIE: Hi. I'd just like to disclose that Puma paid for me to travel here today. My name is Leslie Lurie, and I am Fern Gerard's sister, and I'm going to tell you the effects of neratinib on her life.

Last summer, my parents came to live with my

sister to help her, as her health was deteriorating. Over the next six months they were with her, and her breathing got worse, she was coughing a lot, and needed to be on oxygen for longer and longer periods.

My other sister Tammy then went to stay with Fern in late November and early December, and she continued to deteriorate. I then visited my sister at the end of 2016, and in the time I was there she was on oxygen 24/7 and could hardly get out of bed. She had severe edema and looked like she was 9 months pregnant. She was coughing constantly, and we knew she was dying. We discussed where her kids were going to go and what she wanted for a funeral. It was a horrible time.

Around this time, Fern who reads up on all the new studies and drugs available worked with her doctor and got access to neratinib under compassionate use. She phoned me in early January and told me that she could feel that the drug was working. She told me the edema was getting better and her coughing was greatly reduced.

Then about a month ago, I flew down to Los Angeles, and my sister is no longer on oxygen. The woman who could not walk up the stairs walked a mile and a half with me to go get morning tea and coffee. She is now driving her car, picking her kids up from school, and doing shopping. She has the energy to discipline and be fully engaged in her family's life -- discipline her kids and be fully engaged in her family's life.

This drug has given my sister not only her life back, but her quality of life back. It's such an easy process, no traveling to do long infusions, just 6 little pills a day. I know every person in different, and this drug may not work for everyone, but it worked for my sister. And if it can work for even just a small percentage of women, they should have the option to choose this.

My sister is living proof that this drug works, and I want to thank all the people that have ever been involved in its development. Please make this available so that more breast cancer survivors can have a shot at getting their lives back. Thank

you.

DR. RINI: Thank you. Speaker number 7?

MR. GERARD: Good morning. I would like to disclose that Puma did pay for my travel expenses. My name is Andrew Gerard. I am not a patient, not a doctor. I'm Fern's proud husband. We've been married under four years, less than half of her nine-year struggle that she's had with her stage 4 breast cancer.

I call my wife the compassionate warrior, warrior because having cancer means she fights a relentless battle 24/7, and compassionate because Fern cares about others cancer journeys as much as her own. Fern's dream is to build a career out of helping other cancer patients.

Fern's tried all of the main treatments: surgery, so many chemos, brain radiations. Two of these worked fairly well, but they were stopped due to compounding side effects. All the others did nothing at all or allowed cancer progression.

Fern has been on neratinib now since December 23rd, so far with zero diarrhea, and the

only detectable side effect, fatigue. With neratinib, our family's cancer journey direction has been completely reversed. She has gone from being on her death bed, to living a quality life again.

Before neratinib, my daily roll included carrying Fern upstairs nightly, making sure her oxygen was ready for use, preparing meals, massaging the edema in her legs, watching helplessly as Fern's 4 cancer markers skyrocketed and her resting heartbeat shot past 110. Fern also lost interest in eating due to losing her taste from the full-brain radiation. Fern told me, "I'll never be walking normally again," because it was so painful.

Since December 23rd, watching neratinib work inside of my wife has been simply amazing. Fern now goes up and down the stairs with ease; has no oxygen, not needed oxygen at all; cooks food; drives anywhere; has her normal heartbeat back; and all of her cancer markers have dropped significantly, 3 of the 4 of them back into the

normal ranges. On neratinib, my wife is living her highest quality of life that I've seen.

Being Fern's husband gives me the blessing to learn that anyone may have or get cancer, everyone needs the best treatment options, women fighting this HER2 cancer respond uniquely to each drug, this is not a one drug cures all cancer.

This drug has completely changes our lives. Thank you, neratinib, and thank you to everyone in this room, ODAC panel, oncologists, the public, and Puma Biotechnology. Thank you all for seriously supporting neratinib's evolution.

DR. RINI: Thank you. Speaker number 8?

(No response.)

DR. RINI: Is speaker number 8 here?

MS. FRANKLIN: Hi. I'm Kandi Franklin. I want to disclose that Puma paid for my travel expenses.

In July of 2013, I was diagnosed with breast cancer, and I was HER2-positive. I was treated with chemotherapy and Herceptin, had surgery and reconstruction, and 6 weeks of radiation. Thanks

to my exceptional oncologist and his medical team, in 2015 I participated in the neratinib trial and finished in 2016. I'm here today to share my perspective as someone who took the drug.

I was one of the participants that did not have severe side effects, specifically the diarrhea. In fact, I was taken off of the loperamide shortly after I started the trial because I didn't need it at all.

I have a full-time job, I'm a mom of two teenagers, and an avid jogger. During the trial, I worked full-time. I was active at home with family, and I actually ran two half marathons. And not to boast, but I had some of my most competitive times. To me that means not as slow as normal.

My point is this drug did not prevent me from living my life like I did prior to my diagnosis. There's another woman in my hometown that participated in the same study, and she had a very similar experience to mine. We are just two of many cancer patients that have tolerated the drug very well. It is vital that you equally

recognize those of us that have had a very positive experience taking this drug.

Time and quality of life are probably two of the most important things to a cancer patient. In comparison to the other treatments I've had, what I like about neratinib is I didn't have to be hooked up to anything or go anywhere to be on it. I took my pills in the morning every day and went about my day as usual.

I know this drug's not for everyone, and there are serious side effects for some. Treatment that works for one person may not work for another, but options are important when you're told you have cancer. I refer to this as searching for the bear. Let me explain.

There's a short story that was posted on the internet a couple of years ago. The story was so good, it lingers with me today. It was written by a woman named Caitlin Feeley. In an entertaining way, she likens going through cancer treatment to being chased by a mountain lion. The only thing that can possibly kill a mountain lion is a bear.

She describes what the journey is like finding the bear. Once she finds the bear, she explains that the bear has to go through her to get to the mountain lion to try to kill it, and how brutal that can be.

I highly recommend reading if you want to have a full appreciation for my perspective today. It sheds a brighter light on fighting cancer, the fear and anxiety that goes with it, the reality of treatment, and the importance of having options or more bears.

Let me wrap up by letting you know I was excited to make this trip here all the way from Ogallala, Nebraska to speak to you and let you know personally how important this drug could be to cancer patients like me. The development and approval of new drug options is so vital to our continued survival. Thank you for your time.

DR. RINI: Thank you. Speaker number 9?

MS. LANDHERR: Hi. My name is Allison Landherr, and I would like to disclose that Puma paid for my travel expenses to be here.

At the age of 39, I discovered a lump in my breast that led to a diagnosis of stage 3 triple-positive breast cancer with 5 positive lymph nodes. There's nothing more frightening than being faced with a life-threatening diagnosis with a husband and three young children at home to care for. I immediately went into fight mode and just wanted a plan to beat this disease.

After completing chemotherapy, a double mastectomy, radiation, and a year of Herceptin, I was finally done with 2 years of treatment. I will never forget what my oncologist said to me when I asked her what now? She said live life as if it's never coming back, but every day is precious. I assure you this is a scary way to live, and all cancer survivors worry about if or when their cancer will come back.

My primary concern as a stage 3 breast cancer survivor is my high risk of recurrence. I was fortunate to have an oncologist who was willing to open the clinical trial at City of Hope, allowing me to take this extended treatment with

neratinib. I completed a year of neratinib in November of 2016.

I am so grateful I had the opportunity to take this drug. Neratinib fills an important unmet treatment need, especially for someone like me with triple-positive breast cancer. I made the personal choice to actively fight to decrease my risk of recurrence and improve my hope for extended survival.

The side effects of neratinib are well known, and I was extensively educated on what to expect and how to address the symptoms. I found the side effects to be completely manageable, and they did not negatively impact my quality of life. I was able to maintain my normal busy family activities and work full-time as a physical therapist throughout my treatment.

My choice to participate in the neratinib clinical trial was an easy choice for me. I would absolutely take this drug again despite any of the side effects. They were insignificant in comparison to what I had already endured in my

fight against breast cancer.

As a survivor, I want nothing more than to know I have a fighting chance to beat this disease. I want to be there to see my three incredible children grow into adulthood, I want to know their children someday, and I want many more years with my husband and family.

All HER2-positive breast cancer survivors should have the option and choice of taking neratinib. With FDA approval, this drug could be made widely available to reduce recurrence and extend hope to breast cancer survivors. I strongly urge you to approve this drug so that others have the same access and hope that I had by taking neratinib. Thank you.

DR. RINI: Thank you. Speaker number 10?

DR. BOSSERMAN: Hi. I'm Linda Bosserman. I'm an assistant clinical professor at City of Hope and also on the board of directors. I'm here in neither of those roles. I'm here as an advocate. I had travel funding from Puma. I have no other funding from them, nor do I have any financial

conflicts.

We've heard the science. We've heard this drug reduces recurrence risk in women at high risk. We've heard the side effects are manageable with very intensive education and management, which is what we do every day in oncology.

As an oncologist for 30 years specializing in breast cancer and now value-based care, we have conversations with our patients like Allison about their risk and their potential risk of reduction, and individual patients can make individual treatment plans with their physicians when these drugs are available.

The reason I took my vacation to come here is that Puma has been one of the most advanced companies in providing extended access. But extended access is essentially opening an individual clinical trial at your institution, and I'm very grateful the be at City of Hope where their organization was will to take on hundreds of hours of unfunded work to open extended access so that Allison could have that drug for a year

provided at no-charge by Puma.

My 28-year-old mother of three, who had to move to the Midwest however, had 5 months left on her adjuvant Herceptin for a high-risk triple-positive disease, and at a major national cancer institute in our country, they would not open that trial. And she, 8 months into when she would have been on neratinib, relapsed.

Whether or not it would have helped her, we will not know, but she wanted that drug, and she couldn't have access because she didn't live in the right place to get it. So even with a country making it available, extended access is not the answer.

I really am here to encourage you to approve this drug based on it meeting a phase 3, randomized clinical trial, placebo controlled, our gold standard for FDA approval, so that women and their physicians can make individual decisions on reducing their recurrence risk and deciding themselves whether the side effect profile is acceptable or not, what their recurrence risk

reduction will be, and if it doesn't work, it's a pill. You can stop it.

So your decision today will have a major impact on patients throughout the country, and they are capable of making those decisions individually with their physicians, and your approval will be key in that. Thank you.

DR. RINI: Thank you. Speaker number 11?

MS. KUHNS: Good morning. My name is Kara Kuhns. I would like to disclose that Puma Biotechnology paid for my travel expenses. Thank you for allowing me to speak with you today.

At the age of 34, I was diagnosed with HER2-positive breast cancer in April of 2012. After being diagnosed, I began aggressive treatment at Barnes Hospital in St. Louis. My husband or a family member and I had to make a 2-hour drive to the clinic every week throughout the summer. It was exhausting. I then had surgery and radiation following the chemo.

These treatments seemed to be successful. Then two years later, I presented with an

excruciating headache and learned that I had a brain tumor. Then, the next winter after experiencing another severe headache, I was diagnosed with leptomeningeal disease. This news was absolutely devastating.

We sought out and I participated in two clinical trials, which failed for various reasons. I also received traditional treatments, including high-dose methotrexate. It was extremely taxing for my family because of the lengthy hospital stay every other week. It was distressing being separated from my family.

After this grueling treatment failed, my oncologist suggested neratinib. I began my first dose of neratinib in March. I have now been on it for almost three months. It was a welcome relief to be able to receive treatment at home or on a family weekend away from home. I have had very mild side effects, which were well controlled with medication and did not interfere with my daily activities.

By the end of April, three months after

starting neratinib, the imaging showed a significant reduction in tumor size. Unlike other chemotherapy medications, taking neratinib has allowed me to maintain a good quality of life due to the convenience and accessibility of the tablet. The tablet form of neratinib has allowed me to adhere to an optimal chemo schedule while giving me the freedom to care for my family, including my husband and two young daughters.

I am here to support the approval of neratinib. Approval of this drug would provide other patients the opportunity to benefit from this affective treatment of cancer without the troubling side effects usually associated with chemotherapy.

DR. RINI: Thank you. And speaker number 12?

MR. KUHNS: Good morning. I would like to disclose that Puma Biotechnology paid for my travel expenses for this meeting.

Thank you for allowing me to speak today. My name is Johnathan Kuhns, and I'm the husband of Kara Kuhns. Over the last five years, I've had the

honor of serving as the primary caregiver in my wife's battle against metastatic breast cancer. During that time, she has undergone many traditional chemo treatments, radiation treatments, and has also been involved in clinical trials.

We have two young daughters, ages 9 and 6, and one of the biggest obstacles during these treatments was keeping Kara close to home and keeping our family of four together as much as possible. I'm a firm believer that a family that stays together is best for the raising of our children and also caring for my wife.

There were two very important advantages that we felt neratinib had over previous treatments. First, it was the effective control it showed in trials, and second was the ability to administer it at home with no hospital stays.

Over the last five years, she has spent a lot of time in the hospital for treatment, as well as treatment-related side effects that were not expected. She was accepted in a clinical trial in Boston at Dana-Farber that required a week in

Boston away from our children, as well as many other travel and associated expenses with that.

Less than 2 weeks after her first dose, she began having severe liver complications. Kara was hospitalized for several days at Northwestern Medical in Chicago and was also released from the clinical trial.

After being released from the trial, her oncologist prescribed a regimen of IV high-dose methotrexate, which required approximately 4 to 5 days in the hospital every time she received it, every other week. It also involved home health nurses coming to our home to administer the specific drug to help clear the methotrexate from her system.

Kara was approved in February to be part of a compassionate use study for neratinib. Her latest scans in mid-April showed a significant reduction in tumor size and number of tumors. Since her starting neratinib, Kara has had very few side effects related to the neratinib. Her ability to maintain her quality of life as well as to enjoy

time with our daughters and myself is of the utmost importance to our family.

I would like to reiterate that neratinib's tablet form and effectiveness would greatly impact a cancer patient's quality of life, as well as a caregiver's ability to take care of their families. One of the most important parts of cancer treatment is trying to maintain a somewhat normal life during treatment, and neratinib allows that to happen. It also greatly lowers the unforeseen extra travel cost, et cetera, associated with the current chemo treatments that many people encounter.

I'm a firm believer that neratinib should be approved so that other cancer patients, as well as caregivers for those cancer patients, can experience not only a drastic improvement in their quality of life, but also their ability to spend as much time as possible with their loved ones. Thank you.

Clarifying Questions (continued)

DR. RINI: Thank you. The open public hearing portion of this meeting is now concluded,

and we will no longer take comments from the audience. The committee will turn its attention now to the task at hand, that is careful consideration of the data before the committee, as well as consideration of the public comments.

Before we get to the actual question, I know the sponsor had some responses to questions that came up this morning.

MR. AUERBACH: It was earlier discussed, the time from completion of trastuzumab to entry in the ExteNET trial. So the intent-to-treat population was patients who were up to 2 years from the completion of trastuzumab until the start of neratinib. Obviously, this is something we look forward to working with the agency on with regard to a specific label, but I just wanted to clarify that point.

In addition, Dr. Cole had asked a number of questions regarding tumor size, et cetera, and Bin Yao from Puma Biotechnology has that information.

DR. YAO: Dr. Cole, you had asked a question about prognostic factors between patients who

dropped out early versus patients who stayed on, and we showed the key prognostic factors earlier, and then it showed that they are probably comparable.

Then you asked a question about tumor stage and some other factors, so we now have the data. I don't have them in slides, but if you bear with me, I'll read them out for you.

In terms of tumor stage, the T1 stage for patients who drop out early as a group, neratinib plus placebo combined was 37.9 percent in the patients who dropped out early, and then in the patients who stayed, the T1 stage was 31.3 percent.

I'll offer another variable, which was discussed earlier. That's the staging, TNM staging. In terms of the patients who drop out early, stage 1 was 13.8 percent in the patients who dropped out early, and in patients who stayed, stage 1 was 10.1.

Maybe my last variable I share with you is the nodal status. In the patients who dropped out less than 3 months node-negative was 28.7 percent,

and in the patients who stayed, node-negative was 23.4 percent.

So, as you can see on these prognostic factors, they are broadly comparable. I hope that answers your earlier question.

DR. RINI: Okay. Are there any other questions from the committee to the sponsor that didn't get able to be asked this morning? Please?

MS. PREUSSE: A quick question. Puma is simply requesting approval of neratinib in early-stage disease not in metastatic breast cancer; is that correct?

DR. RINI: That's correct.

So, we'll now -- go ahead.

MS. PREUSSE: And by stage -- sorry -- early-stage, all of stages 1, 2, and 3. Right?

DR. RINI: Early-stage breast cancer, correct. Dr. D'Agostino?

DR. D'AGOSTINO: There was a mention about overall survival. The rates here are quite high and what have you. There are statistical differences between the placebo and the drug with

respect to the recurrence.

Do we have to be concerned at this point with overall survival in terms of making a decision? I've been occasionally on the panel, as you know, and there are times when we have talked about accelerated approval based on progression-free survival, but then we have to go on to overall survival.

Is that discussion pertinent to this drug?

DR. SINGH: We do not require overall survival benefit at the time of approval. It was brought up as a point in the context of prior adjuvant therapies, but I do not believe that it is necessary or should necessarily be incorporated into this decision.

DR. D'AGOSTINO: I'm not asking so much about -- well, I am asking you about the approval. But is it lurking in the background that if this is approved, overall survival has to be looked at?

DR. PAZDUR: Yes, we will look at it, definitely, to make sure there's no decrement in overall survival. That's for sure.

DR. D'AGOSTINO: Thank you.

Questions to the Committee and Discussion

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

I'm just going to read the question to you. Is the risk-benefit profile of neratinib sufficient to support treatment in the proposed indications as a single-agent for the extended adjuvant treatment of adult patients with early-stage HER2 overexpressed or amplified breast cancer who have received prior adjuvant trastuzumab-based therapy?

I'll first ask the committee if there are any questions about the question's wording or clarification. Dr. Nerenstone?

DR. NERENSTONE: Because this may become a question of risk-benefit for the patient and the physician, do you ever require the package insert to give the information that we have, so that we

can make that decision?

Second of all, probably more importantly than -- the way it's done there I think is a little confusing. Node-negative is really -- they don't say whether it's stage, and most oncologists think about stage.

So node-negative is not node-negative. It could be a T3 node-negative. So could we ask them, if we decide to vote, that the package insert shows those subset analyses as well, so that there could be more information about the particular risk-benefit per patient?

DR. BEAVER: Yes. We're interested, in terms of the question, in the overall population, but certainly we'll take comments associated with the vote into consideration.

DR. RINI: Dr. Klepin?

DR. KLEPIN: I just wanted to clarify again, the proposed indication that we would be voting on, does that include the intention to treat time, so the 2-year time frame that was part of the eligibility from -- meaning that we're not voting

to say, yes, if you had trastuzumab 5 years ago, you would also be eligible, or is that not included at all?

So is this any time in the past or specific to the eligibility of the intention-to-treat population, which was the 2 years?

DR. RINI: I think as per the previous question -- and the FDA can comment -- the indication is as written on the screen. Obviously, in the discussion of your vote, you can comment on that.

Was there a question over here? I'm sorry. Sure. Ms. Spears.

MS. SPEARS: So I'm still struggling with that risk-benefit and the broadness of the indication. I realize we want our doctors to be doctors. I mean, definitely that's it. But once you open that door, it'll never shut.

I see that this drug could be very beneficial, and I'd like to see it pursued in the metastatic setting for sure, from what we've heard and what we've seen before, but this opens the door

very broadly. That 2.5 percent and the 95 percent, when you're already at 90, and then you've gained just a little bit, that's hard for me to say that that's clinically relevant.

Anecdotally, we as patients -- I'm an 18-year survivor of HER2-positive without trastuzumab. I was pre-trastuzumab. As a patient, you want to try everything, but you also don't want to do false hope. And I have a feeling that for some patients it might be that false hope that's going to drive them to take an extra medicine. And I think we've fallen into that trap before in a lot of other indications. So I'm still kind of struggling with the broadness of the indication.

DR. RINI: Okay. Other comments about the question? Down there?

DR. MINASIAN: I would echo Patty Spears' comments about the broadness of the indication. What we have seen in one year of neratinib followed by the one year of chemotherapy and trastuzumab.

I would also express concern about having this broad blanket, particularly as it pertains to

those patients who have had a longer time since trastuzumab, receipt of chemotherapy, so that the 2-year eligibility for the protocol makes a lot of sense for this. Even though, as we look at the data, the subset analysis for those, between 1 and 2 years, is I would say concerning, but I can appreciate that that was a subset. So, the 2-year time frame as protocol directed makes sense.

I'm also surprised, but maybe not, by the wording of adult patients and wondering whether or not the population on the study that we've evaluated, with the 2800 patients, included any men or it was solely women with HER2-positive breast cancer.

DR. RINI: Okay. Thank you. Any other comments from anybody who hasn't spoken yet?

(No response.)

DR. RINI: So I think we can proceed with our vote. We'll be using an electronic voting system for this meeting. Once we begin the vote, your buttons will start flashing and will continue to flash even after you have entered your vote.

Please press the button firmly that corresponds to your vote. If you are unsure of your vote or wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen, and Lauren will read the vote from the screen into the record.

Next, we will go around the room and each individual who voted will state their name and what their vote was, and also importantly you can then discuss the reason why you voted how you did for further discussion around the questions.

Please press the button on your microphone that corresponds to your vote. You have approximately 20 seconds to vote. Please press the button firmly after you've made your selection, and the light may continue to flash. Again, if you are unsure of your vote or wish to change it, just press the corresponding button before the vote is closed.

(Voting.)

DR. TESH: For the record the voting result; 12 yes, 4 nos, zero abstentions, zero no votes.

DR. RINI: Now we'll go around the table and have everyone who voted state their name, what they voted, and any discussion that want to give around the topic or why they voted how they did. And we'll start with Dr. Morrow, again down at the end. Oh, she's not voting.

We'll start with Dr. Lipkowitz. I'm sorry.

DR. LIPKOWITZ: Stan Lipkowitz from NCI. So I voted yes, as shown. I think I have a lot of the same concerns that you've heard. The drug clearly has efficacy in HER2-positive breast cancer based on metastatic neoadjuvant and now this intention-to-treat analysis from a post-adjuvant study. At the same time, it has -- so there's clear benefit to it. It's an unmet need in terms of patients who relapse after neoadjuvant or adjuvant chemotherapy.

There's clearly toxicity associated with this drug and a significant number of patients won't continue it, and that's something that is

concerning. And as you heard it can be managed. I should point out, if you look at the percentage of patients who stop an AI for example, it's not that different. So when we think of extended adjuvant endocrine therapy, for example, we're faced with some of the same questions of risk versus benefit and similar benefit as well.

There are some unknowns that concern me. And again, this goes back -- I'm voting on what we were given, but there's a broad indication here, which as an oncologist I would have to have thoughts about which patients would I treat. And I don't think I would treat as broadly as the indication describes.

There are some pre-specified but exploratory analysis that suggests that high nodal status or ER-positive status may be the patients who benefit most. And that's interesting since the ER-positive patients are the ones who may not benefit as much from the chemotherapy given with the trastuzumab.

It would be nice to have more data that gave us predictive biomarkers or some predictive

indication, if you will, for who should be treated, and that's something I think that would be very important going forward.

So at the end of the day, I thought it would be useful to have in patients who I might be worried are at high-risk of recurrence and fit perhaps either 3 or more nodes or more than 3 nodes or ER-positive.

There are a couple of unknowns here. One is that in one of the slides that blew by us, they had in their forest plot, the patients who got neoadjuvant therapy, who represented about a quarter of these patients, didn't seem to benefit. And that's a curiosity. Was that because they were all ER-negative? What was different about that group?

The second is we're entering the age where virtually all of the high-risk patients are probably going to get pertuzumab, and does that impact the benefits seen to this drug? I don't know the answer to that. So I think there are a lot of factors that will figure into a discussion

with patients. But at the end of the day, I think it's useful to have this as an option to treating patients.

But I think it's very difficult a decision to decide who I would and would not recommend this for, and for the patient to decide whether they would or wouldn't take it for what is essentially a small percentage of patients who benefit.

DR. RINI: Thank you for that.

Dr. Minasian?

DR. MINASIAN: I did vote yes as well for similar reasons. I think the option should be available. While the analysis was complicated by lots of different factors, I do think, as Dr. Burstein said, that the company did a heroic effort in at least reconsenting and gathering as much data as possible.

I remain concerned that the indication as stated is far too broad. And while I agree with Dr. Lipkowitz that the data points to different subsets, I think we need greater understanding of which subsets of patients would be most responsive

to this therapy. But at the same token, I recognize that having the option available is an important one because we don't right now have a good way to preidentify those who will benefit.

DR. RINI: Thank you. Dr. Royce? Dr. Nerenstone, I'm sorry.

DR. NERENSTONE: I also voted yes and just want to reiterate about the package insert. I'm also hoping that this is not being used as a backdoor way to get approval for metastatic disease. I think for those of us who treat out in the community, the indications are looked at by the drug company. I think this is probably a very effective drug in a certain situation and would urge the company to pursue that indication as well so the sake of our patients who otherwise will not be able to get drug.

DR. ROYCE: I voted yes as well for very similar reasons. There are patients who will benefit from this. Unfortunately, we really do not know and can't identify who are those patients. I think it would be very important to identify two

points; one, that this is not for all patients who have received trastuzumab, we should be very strict about the duration since the time of trastuzumab less than one year. And number two, if it were at all possible to co-package this with the antidiarrheal, because, in terms of cost for the patient, the antidiarrheal would be an added cost.

DR. RINI: Thank you. Dr. Seidman?

DR. SEIDMAN: I also voted yes. There's no exclamation point after my yes. It's just a yes. I think that the trial met its primary endpoint. I'm happy that the result looks durable through 5 years. I'm reassured by the rigorous statistical analyses that were applied given the changes in study design along the evolution of the trial.

I do think that physicians will select patients very carefully for using this, and I think that ultimately, if approved, it will need to be considered in the current landscape of other options that are and may be emerging.

DR. RINI: Thank you. Ms. Spears?

MS. SPEARS: And I voted no. I voted no

mainly because of the broadness of the indication. I think it is important to get drugs out to patients, and I think this will benefit a certain subset of patients. I'm just not sure we know which ones yet. And what we do is tend to put a lot of patients at risk to benefit just a few. We do that a lot.

I think that we're also putting a high expectation on the oncologist and not everybody's a Hope Rugo, which I adore -- but not everybody is so thoughtful. And I think that this will be something that will be just tagged on to the end of trastuzumab in many cases. And the education that's going to go along with the added side effects I think is not going to be equally distributed as well.

I think access to that education is critical as well during this, and I don't want to give that false hope as well to patients in if you've got stage 1 of HER2-positive, do you really need this drug? So that's why I voted no.

DR. RINI: Thank you. Ms. Preusse?

MS. PREUSSE: I also voted no. I really struggled with this decision, especially after listening to the patient representatives in the audience. Every story does matter, every patient life does matter, but we are, as Patty stated, very eloquently proposing this for a very wide swath of patients.

To me, it feels like it just needs to go back in the oven and cook a little bit longer. It's too broad. It's not enough -- too much preliminary data. And the added benefit above what already exists is just not compelling.

DR. RINI: Thank you. Dr. Uldrick?

DR. ULDRICK: Yes. I voted yes as well. The study met its primary endpoint. I was impressed by both the analyses from Puma and the FDA, the sensitivity analyses supporting the primary outcome. The absolute benefit is comparable to that of other adjuvant therapies that have been improved, and I think that the severe toxicities are reversible and potentially manageable. And that's why I voted yes.

DR. RINI: Thank you. Dr. Cole?

DR. COLE: Bernard Cole, I voted yes. I felt that the study had a number of important advantages. It has a large sample size of 2840. Treatment was blinded. There was independent monitoring at multiple levels, and there was an honest attempt to obtain longer term follow-up, and it was largely successful.

These are hallmarks of a study designed to minimize bias and achieve a reliable result. The primary analysis of the ExteNET trial indicated a benefit for neratinib with a statistically significant hazard ratio of 0.66.

Unfortunately, as we discussed there were several concerns about how that trial unfolded. There were multiple adaptations, differential dropout, differential reconsent. These all have the potential to inject bias into the efficacy analysis or affect the generalized ability of the results in light of the proposed indication.

The sponsor and the FDA did provide helpful sensitivity analyses to address these issues.

Although I would have liked to see a more thorough analysis along these lines, I do believe it unlikely that such analyses would appreciably expand the range of plausible hazard ratios given the ExteNET data and as described in the sensitivity analyses that were done.

Finally, I would like to commend the sponsor for the attempt, and the largely successful one, to obtain longer term follow-up, as well as for engaging their external experts to help address the trial's limitations. The sponsor was handed a trial essentially that had these limitations already built in, and there was a challenge in addressing them and bringing something forward that would lead to this meeting. And I think they did a good job along those lines, and most of all engaging those external experts, not only that, but also listening to them.

DR. RINI: Thank you. Dr. Burstein?

DR. BURSTEIN: Harold Burstein, Dana-Farber. I voted no. I want to first speak to several of the public speakers, who I think really gave

compassioned instances where I might like to use this drug in the setting of refractory metastatic disease with certainly compelling clinical experiences, and in the case of a stage 3 ER-positive HER2-positive breast cancer where I am convinced that there is a signal of significant benefit there. And I'm glad that this patient had access to the drug, and I think other patients might benefit in that context as well.

The question we were asked was whether there was risk-benefit that was sufficient for stage 1, 2, and 3 breast cancer, and my interpretation of the data was that that was too broad a suggestion. In particular in the setting of stage 1 or node-negative breast cancers or in the group of ER-negative breast cancers that are also HER2-positive, I was not persuaded that there is a clinical signal of activity that would certainly justify even modest side effects, which were documented.

I appreciate the point that these are generally reversible and the patient and their

medical team can choose, but were shown to affect quality of life somewhat adversely.

I will also add, because it could be relevant to discussions in the future, that I was not persuaded that the neoadjuvant data or the data from the existing literature on metastatic disease showed a signal for activity for this drug.

In the only randomized experience in the neoadjuvant setting, the drug did not outperform existing standards of care. And to date in the metastatic trials, there has been no compelling signal of activity that exceeds that available with standard treatments, though I take the point that we've certainly heard some dramatic personal testimony today that speaks to an opportunity to explore the drug there.

So based on those considerations, I felt that the indication as purposed did not suggest a risk-benefit profile for the majority of patients we see in the United States who are diagnosed with HER2-positive early-stage breast cancer.

To elaborate on that just briefly, me and

others have recently shown that stage 1 tumors in particular have an outstanding prognosis, 96 percent 7 year disease-free survival recently reported. And I think it's hard to imagine really improving on that with an indication for this agent.

Finally, I did have lingering concerns about the standard of care that the patient's received. This was a global study. Patients across the world are not always treated in the uniform fashion, which is understandable. And in fact, in many instances that's power to a large randomized trial showing the robustness of the opportunities for improvement.

But at the same time, for women in the United States who would be receiving concurrent chemotherapy and trastuzumab, who in the vast majority of instances would be receiving AI-based therapy and might be receiving slightly more effective chemotherapy regimens, I thought this weighed enough against a relatively narrow benefit that it made the calculation harder.

DR. RINI: Thank you. I'll save my comments to last so I can summarize. Dr. Nowakowski?

DR. NOWAKOWSKI: Greg Nowakowski. I voted yes for the reasons similar to which were already mentioned. I believe the drug did show a signal of benefit in the materials presented by the applicant, and the efficacy signal was maintained in a number of sensitivity analysis, which were done by the FDA.

The benefit of the drug in the absolute number is relatively modest if you consider toxicity, so it does come with a significant price in terms of toxicity, but the toxicity is not sustained and appeared to be manageable. Importantly, the applicant appears to be already developing strategies how to mitigate this toxicity.

I also had the same concerns in regards to label and broadness of the label, but I believe this is a conversation which can be left to the wisdom of a treating physician and a patient in terms of the possible magnitude of benefit in

patients with stage 1 disease or low-risk disease.

The same about the time frame, in my clinical experience for patients who are in remission for considerable duration of time over 5 years, it will be unlikely that this would be a significant consideration in changing therapy at this point. So overall, for those reasons I voted yes.

DR. RINI: Thank you. Dr. Riely?

DR. RIELY: I voted yes. I think it's clear that the magnitude of benefit observed in this trial is modest. Aside from hormonal therapies, there had been no approvals with such modest absolute differences and disease-free survival at 2 years. So I think these are modest differences, but I was reassured by all the FDA analyses that this is a statistically real observable phenomenon.

Unlike some of the others, I was actually swayed by the efficacy in the neoadjuvant setting, as well as the metastatic setting that this is an active agent, and so it's likely to lead to benefit for patients.

I'd like to end with two comments; one, supporting the first public comment that we really ought to be aiming for higher differences or higher benefits in the therapies that we develop because this is better for our patients and we want that.

Then finally, I'll say I hope that physicians, if they have access to this, that they do put a lot of thought into this. Just as importantly, those who develop guidelines have to think about the data that we've seen today and incorporate a lot of the information we've seen today into how we actually use some of the drugs that are available.

DR. RINI: Thank you. Dr. Klepin?

DR. KLEPIN: Heidi Klepin. I voted yes for all the reasons that were already mentioned, respecting the limitations that we've discussed at length. I particularly felt that it was important to support this indication because this is an unmet need, and I think the outcome that was -- the primary outcome is an important and relevant outcome for our patients even though what we're

seeing effect-wise may be modest.

I also voted yes because it was an all or none vote, as I interpreted it, but I would strongly recommend that the indication be restricted to the eligibility of the trial specific to the 2 year from trastuzumab completion.

I think that's really important. I know we weren't allowed to change the indication in our vote, so I voted yes. But I think that is very important. We saw no data to support using this drug in people who are past that time frame, and therefore I wouldn't feel comfortable with the safety and efficacy in that setting.

The other thing I would just say to the investigators and the sponsor, as much as possible, if you can provide a lot of the additional analyses that you showed us with respect to the subset analyses, with respect to toxicity, and efficacy in your effort to dissemination, I think that's going to be so important for investigators. Particularly in the manuscripts, that's where most physicians are, looking at the manuscripts and making a

decision based on that. And the more data that you can provide to help individualize that treatment decision-making is going to be really valuable given the broadness of the indication.

DR. RINI: Thank you. Vali?

DR. PAPADIMITRAKOPOULOU: Yes. I voted no. My name is Vali Papadimitrakopoulou. The reason I think was already outlined by Dr. Burstein because he's the expert in this disease, and I am not.

I think the benefit needs to be there, and it needs to be clinically meaningful. We didn't see from the overall population that this is clinically meaningful. I think for a subset of patients, they were outlined as maybe the HR-positive patients or other subsets. This may be true, but I think voting yes the way the question is posed means that I totally embrace the data for all the patients, and I don't think the data pointed in this direction.

DR. RINI: Thank you. Dr. D'Agostino?

DR. D'AGOSTINO: Ralph D'Agostino, I voted yes. Most of what I was going to say has already

been said. But just to repeat, the results were statistically significant, modest in terms of the magnitude but consistent. And they were robust over all the sensitivity analysis. Within the subgroups, they seemed to be robust, and they extended to 5 years. So I think we have a really durable, not huge, result here that is they say significant, and my vote was very much tied to that.

The safety profile is a little issue obviously, as was brought up a number of times, but it's not an unsafe activity. So I thought it made a lot of sense to take the data, put it together in terms of the statistical significance, its robustness, its ability to extend to a group of a number of different subgroups, and a yes sounds appropriate to me.

Adjournment

DR. RINI: Thank you. Brian Rini. I voted yes. Just to maybe summarize what's been said around the table, I think what we heard was that there are concerns about toxicity, obviously

specifically diarrhea, a good point about access to equal education about that toxicity and impact on quality of life.

I think for me I thought the sponsor provided some compelling data about the toxicity being relatively early, relatively manageable, and short-lived. And as I tell my patients, you give your consent every day to get treatment, so you can stop, and the toxicity goes away. So obviously, that's an ongoing risk-benefit analysis.

There was some concern expressed about the changing landscape of adjuvant treatment and who these patients were, and do they represent what's going to be in current practice moving forward. There was concern by the group, and I share that there was a relatively modest effect here, although I think it's in the range of other drugs in the adjuvant setting.

I think for me probably the most compelling was just the consistency both within and across analyses from both sponsor and FDA that that small benefit was real and potentially durable. However,

noting toxicity, the number needed to treat to prevent one recurrence would be very high. We weren't given that number, but that I believe would be quite high.

Then I think a consistent concern from everyone, and I share it, is about the label being too broad and about the subsets of time since prior adjuvant trastuzumab, hormone receptor-positive, subsets node-positive, what have you, and a mix of patients with a very broad label.

I think you heard that loud and clear for further discussion. But again, I thought there was a small but real benefit, and I think that's where the committee came down, and that's why I voted yes.

So if there's no other FDA comments, we'll now adjourn the a.m. session of the meeting. Panel members who are not attending the second session, return your name badge to the specialist outside the room so they can be recycled, take all personal belongings with you.

For those of you who are coming back for the

p.m. session, we'll break for lunch, and we'll be back in this room at 1:00 p.m. to start.

(Whereupon, at 11:55 a.m., the morning session was adjourned.)