Advances in Extended Adjuvant HER2-Positive Early Breast Cancer

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MS. GOFORTH Good evening, everyone. Welcome to the accredited symposium on Advances in Extended Adjuvant HER2-Positive Early Breast Cancer. My name is Paige Goforth and I am a PA at Wellmont Cancer Institute in Kingsport, Tennessee. This symposium is accredited by the Annenberg Center for Health Sciences at Eisenhower. To claim your credit, please follow the instructions on the sheet that you received this evening. If you didn't receive an instruction sheet, let one of the staff members know and they will provide one to you. Tonight we have two wonderful speakers. Dr. George Thomas Budd is a staff physician at Taussig Cancer Center at Cleveland Clinic. His clinical interests include breast cancer, sarcomas, and experimental therapeutics. His research interests are focused on experimental therapies, breast cancer, and sarcomas. Dr. Budd is a fellow of the American College of Physicians and a member of the American Society of Clinical Oncology and American Association for Cancer Research. My dear friend and colleague, Wendy Vogel, is an oncology nurse practitioner at the Wellmont Cancer Institute in Kingsport, Tennessee. She is board certified through the Oncology Nursing Certification Corporation and a certified family nurse practitioner through the American Nurses Credentialing Center. Ms. Vogel is an associate editor of the *Journal of the Advanced Practitioner in Oncology* and is a founding member of APSHO, the Advanced

Practitioner Society for Hematology and Oncology. Please welcome Dr. Budd and Ms. Vogel.

MS. VOGEL Thank, you Paige. Good evening. It is wonderful to see everyone tonight. I hope you've had a wonderful day.

We're very pleased to be here tonight to talk to you about Advances in Extended Adjuvant HER2-Positive Early Breast Cancer. Disclosures are as listed there. Let's talk a little bit about learning objectives. At the end of this activity, you should be able to describe the mechanisms of action of novel extended adjuvant therapies for early HER2-positive breast cancer, utilize evidence-based strategies for prophylaxis of diarrhea and other side effects, optimize patient selection for treatment with extended adjuvant therapies, and implement HER2 testing in accordance with the latest clinical practice guidelines.

MS. VOGEL Here's the outline of tonight's talk that we are going to do. We are going to do a little short breast cancer introduction, we're going to talk specifically about HER2-positive breast cancer, the pathophysiology of that, testing for that, and management. We'll also spend a couple of slides looking at future treatment options and then symptom management as well. We'll also look at the role of the advanced practitioner providers in caring for patients with HER2-positive breast cancers, and we'll conclude with a case study.

Let's talk a little bit about breast cancer. When—you've seen this slide before—when we're talking about new breast cancer cases in the United States in 2017, we are looking at over 250,000 new cases this year. When we talk about mortality, it's estimated that over 41,000 deaths this year from breast cancer. So

if we were to look at prognosis based on staging alone, we can look at a stage I to IV 5-year survival and we see that stage I to 0 is almost 100% 5-year survival.

When we drop down to stage IV, we see that that drops dramatically at 22% -year survival, but there are many other factors that affect prognosis besides staging. Hormonal status, HER2 status, grade and histology, lymph node status, age, health, treatment, and the response to treatment. But tonight we are specifically going to be looking at HER2 status. Breast cancer is not just breast cancer is not just breast cancer; it is a very complex disease and this is kind of a simplified, if you will, look at types of breast cancer. Luminal A, luminal B, HER2 overexpression and basal type, and you can see the differences in histologic grade, distinguishing markers, percentage of the total breast cancer population and prognosis, as well as targeted therapy. We are going to be looking, as we said, to HER2 overexpression tonight. So you can see that generally these tumors have a high histologic grade. We have distinguishing markers that are generally ER negative, PR negative, and HER2 positive. In terms of population of the total breast cancer population, HER2-positive represents about 20 to 30% of these patients.

Prognosis has generally been poor, and targeted therapy now is HER2 targeted therapy that we will discuss tonight. So if we were to take a look at a HER2-positive breast cancer cell and we talk about what is HER2, also you may see it in literature as ERB2. This is a transmembrane tyrosine kinase receptor and it's a member of epidermal growth factor receptor family. The HER2 product is overexpressed in about 18 to 20% of all breast cancers. If you look at this little

picture here, you'll see that a normal breast cancer cell has up to 50,000 HER2 receptor sites, we just have that, but if we are talking about overexpression of HER2, this may have as many as two million receptor sites. So the result of that is a breast cancer cell gone wild. We have excessive cellular division, the tumor learns to have—it loses normal apoptosis and becomes an immortal cell. So it's a very much more aggressive tumor phenotype. It has a poor prognosis, it has a higher rate of recurrence and mortality independent of other risk factors such as tumor grade, age, stage, and so on. So this is a picture of a HER2 pathway.

This is almost a stay-tuned message, and it's so exciting because each of those little blurbs there that you see on the HER2 pathway can represent potential targets that we have for drugs. When we are looking at the HER2 pathway and we have overstimulation of that pathway, the bottom line that we see of the cell gone wild is abnormal gene expression, we have cell motility, and cell cycle progression. Now there is some crosstalk going on here that's really interesting that we see. So when we have HER2 downstream activation, this actually leads to endocrine therapy or hormonal therapy resistance. So we really need to get two bangs for our buck, and we can do that by targeting both of these pathways. When we talk about HER2 targets and we talk about these pathways, these are some of the drugs you can see and where the drugs are represented in this targeted therapy. So we have therapeutic options such as trastuzumab, pertuzumab, we have neratinib now, and lapatinib. So let's talk just a little bit about HER2 testing. There are some guidelines for HER2 testing and those are listed there from ASCO, the College of American Pathologist, and the NCCN. I

will say you have access to these slides after the presentation, so you'll be able to go to these websites and also refer back to the slides. Great late night reading, by the way.

So let's talk about the recommendations for HER2 testing. All patients with invasive breast cancer should be tested for HER2 overexpression. Positive status is demonstrated by protein overexpression or gene amplification. Now if the results are equivocal, in that medium range, then reflex testing should be done with an alternative assay, and we could consider repeat testing if results are still discordant. Labs should be accredited that are doing your testing and should demonstrate high concordance with validated HER2 tests on large and representative status specimens. Just to mention immunochemical testing, which is one of the types of testing that we do on HER2. This is the grading, 3+ is considered positive for HER2 overexpression and what that means is that more than 10% of invasive tumor cells stain positive for HER2. 2+ is equivocal, we don't really know to call it positive or negative. That means that there may be non-uniform or weak membrane staining, but there may be staining in at least 10% of the cells. 0 to 1+ is considered negative for HER2 protein expression. This is an algorithm—thank you, Dr. Budd, for providing this—that talks about HER2 testing and the most recent guidelines for this. We do batch controls, on site controls show appropriate hybridization, so if we have a HER2 ratio of greater than 2 or we can go down the other side and have a HER2 ratio of less than 2. So if it's greater than 2, then we would consider that ISH positive, and if we have less than 2, then we have to look at that a little more carefully, so we

have average HER2 copy number of greater than 6 than ISH positive. If we have an average HER2 copy number of less than four signals per cell, that is considered ISH negative, and if we have in the middle where we have a HER2 copy between 4 and 6, then we call that ISH equivocal. And so then we have to order a reflex test to confirm our results. Now there are also guidelines for the treatment or management of HER2-positive breast cancer; both ASCO and NCCN are listed here for you. So, in brief, treatment of early-stage HER2-positive disease includes several different treatment options that Dr. Budd is going to speak to you about in much more detail shortly.

We can do neoadjuvant chemotherapy. Neoadjuvant means therapy that's given prior to surgery; we want to shrink that tumor down. That is neoadjuvant and that could be done with chemotherapy and trastuzumab and/or pertuzumab. Certainly surgery and radiation therapy may or may not be included in this plan, adjuvant therapy with trastuzumab and hormonal therapy or manipulation. Here are some of the neoadjuvant treatment regimens for HER2-positive breast cancer, and this is from the NCCN guidelines. If you are new to oncology, let me introduce you to the NCCN guidelines. This is the bible of oncology, NCCN.org, and it's the latest and the greatest in the US for treatment of cancers. Now in some of the NCCN guidelines they'll have listed as what is called "preferred," it may also say "category 1," and that is when the experts will be most sure of the data, they agree on it that the most accurate data is there, and that would be considered a preferred or category 1 recommendation. The preferred regimen for HER2-positive breast cancer per the NCCN guidelines is AC followed by T plus

trastuzumab and plus or minus pertuzumab as well as TCH, and there are other regimens listed there for you. So adjuvant treatment regimens for HER2-positive breast cancer if they are hormone receptor–positive would also include adjuvant endocrine therapy plus or minus adjuvant chemotherapy plus trastuzumab. If they are hormone receptor–negative, then we'll be looking at adjuvant chemotherapy plus trastuzumab. Now something that's very exciting that's out is what we call extended adjuvant therapy, and the rationale for this is despite our best treatments for HER2-positive disease, about 25% of women who have been treated with adjuvant trastuzumab have breast cancer recurrences with a median follow-up of about 8 to 10 years.

What we see now is that studies show that longer duration of adjuvant trastuzumab didn't really improve outcome. There is a new drug on the market. The new indication now is for what we call extended adjuvant therapy, and we're going to spend some time talking about that and this new drug is called neratinib. These are the HER2-positive agents for adjuvant therapy for treatment: trastuzumab, pertuzumab, lapatinib, and neratinib. Now I'm going to turn the stage over to Dr. Budd and we'll begin talking about some of the clinical trial data.

DR. BUDD All right. Thank you, Wendy. That was a great introduction. I'll be talking about some of the clinical trials and underpin some of the concepts that Wendy was talking about and we'll be talking about later. And maybe it's just I'm getting a little bit older, but I kind of like to take a historical perspective more and more and find that more and more attractive. So this is the

first kind of clinical evidence looking at HER2 amplification in patients with breast cancer by Dennis Slamon and you can see this was on January 9, 1987, so a good long time ago. And this was done with Bill McGuire who was actually at San Antonio at that time and had set up a tumor bank where he was testing estrogen receptor and progesterone receptor for hospitals all over Texas. And as part of that, he obtained some simple follow-up on those patients, so this was a real resource. And what Dr. Slamon did is he went and tested HER2 on these patients ,and this is what he found, is that the patients who had amplification that you can see here did not do as well as those who were not amplified, and the patients who were highly amplified, as you can see here, did particularly poorly.

Gary Clark who was the statistician on this study made the statement that oncogene amplification was the first prognostic factor that he had seen by itself that was that powerful, so you can see that this is lymph node status and this is HER2 status, so those are the only two factors that were in that range of important. HER2 established itself at that point as a very important prognostic factor, meaning it was a bad thing to have. Now the question is, can we do something about it? And as you know, the rest is history: trastuzumab came out, it was used in metastatic disease, it was quite effective, and so it was only a logical thing to bring it closer to the diagnosis and give it to patients early after diagnosis to prevent or delay recurrence. There are a number of trials done in Europe and the rest of the world. There is the HERA trial. In this country, there were actually two trials ongoing and three eventually, one from the NSABP and one from the US Intergroup, and then the US Intergroup and the NSABP decided

to join forces and do this study looking at trastuzumab plus adjuvant chemotherapy for HER2-positive breast cancer. There was an initial study and then a later presentation. This shows the two trials: NSABP 31 looked at doxorubicin and cyclophosphamide followed by paclitaxel, or doxorubicin and cyclophosphamide followed by paclitaxel with trastuzumab. The US Intergroup was very similar, I think you all are familiar with this trial, but I think its worth going over. Doxorubicin and cyclophosphamide followed by paclitaxel and only paclitaxel was given weekly, doxorubicin and cyclophosphamide followed by paclitaxel weekly with trastuzumab. There was a third arm here in the Intergroup trial that I'll talk about a little bit later and that looked at sequential treatment; in other words, in the NSABP arm seen here, the trastuzumab was given concurrently with the paclitaxel. In this arm, the chemotherapy was all given first and only then was the trastuzumab started, and that was the same design that was used in the HERA trial in Europe, but as time went on, we could see women dying of HER2-positive breast cancer, and there was really a push to get these trials done.

So the thought was why are we doing two trials; we should do one trial, we've got some common arms. So that middle arm was taken away in this analysis, and then the similar arms, the control arms, just chemotherapy alone were grouped together, and then the two arms looking at chemotherapy plus trastuzumab with the trastuzumab given concurrently or begun concurrently with paclitaxel. These were analyzed together in a control in investigational arms. These are the patient characteristics. I'll just point out relatively few of these

patients were node positive, only 15%, you can see here, so this was a higher-risk group. There was this joint statistical analysis, there was an initial analysis, and then later I'll show you this analysis a little over 8 years. This is the first publication, the first analysis that came out in the *New England Journal of Medicine*, quite dramatic effects as you can see here. On the left is disease-free survival, so prevention of recurrence, and it reduced, adding trastuzumab reduced the rate of recurrence by 50%, and reduced the rate at which patients were dying by a third, so quite a dramatic effect.

There was a downside of course in terms of toxicity, and the principle toxicity was cardiac toxicity, so here you can see cardiac events, which was basically heart failure or a significant drop in the ejection fraction, and this was with the chemotherapy alone and with adding the trastuzumab, about 4% of patients who received this anthracycline-based regimen developed some form of cardiac toxicity. Now I'll remind you of that middle arm that I took out of that previous analysis that looked at sequential treatment of chemotherapy followed by trastuzumab, and these next couple of slides look at that. Here we see chemotherapy alone or chemotherapy followed by trastuzumab, and you can see there was a benefit, and this was recapitulated in the HERA trial, which was a much larger trial, and it showed the same thing. But what about comparison of giving the treatment? Beginning the trastuzumab concurrently with chemotherapy or giving it only after completion of chemotherapy, and here you can see the concurrent approach is better, so it's better to begin the trastuzumab with chemotherapy and that's something that's carried on to most of the trials done in

this country. So this final analysis after with a follow-up of 8.4 years, you can see here the results are holding up. On the left is the death rate; the rate of death or mortality was reduced by about a third. You can see that has a ratio of 0.63. The relapse-free survival was similar and has a ratio of 0.46, so a 40% reduction in the rate of death. To summarize, on a median follow-up of 8.4 years, adding trastuzumab to paclitaxel following AC was associated with improvement. It was better to give the trastuzumab concurrently with the paclitaxel, however, with high-risk HER2-positive breast cancer, the disease-free survival rate was reduced by 40% and there was also a reduction in death rate.

Trastuzumab was helpful across the board for HER2-positive breast cancer, but this slide shows a very interesting finding looking at patients who are all HER2-positive, but looking at those who are ER-positive versus those who are ER-negative, and what you can see here in the ER-negative patients there is this kind of a rapid rate of recurrence, but then it slows down. And if you get to 7 years, it was very unlikely that a patient would recur. With the ER-positive patients though—these are the patients who got trastuzumab—there's a more kind of gradual relapse rate and there's no reduction at that 7-year mark, there's nothing magic about it. So this is the difference in the natural history between the ER-positive and the ER-negative HER2-positive patients, and I think it's important to keep that in mind as we talk about extended adjuvant therapy, particularly with the drug neratinib, which is now approved for this purpose. Now that was where we were, anthracycline-based chemotherapy, but I'll bet a lot of you are not using anthracycline-based chemotherapy with trastuzumab and its

because of this trial. Though I'm sure many of you are familiar with BCR-G006 that looked at patients with HER2-positive breast cancer. They got doxorubicin cyclophosphamide followed by docetaxel or doxorubicin cyclophosphamide followed by docetaxel with trastuzumab, and here the trastuzumab was given and begun concurrently with the docetaxel, or a third arm, a nonanthracycline-based arm called TCH: docetaxel, carboplatin, and trastuzumab, with, again, the trastuzumab begun concurrently with the chemotherapy. And the results you see here, the non-trastuzumab-based regimen was the worst, and both of the trastuzumab-containing regimens produced very similar outcomes. So this regimen has become much more popular primarily for this reason. There's a lower rate of toxicity, particularly cardiac toxicity, and a low rate of secondary leukemias.

The cardiac toxicity, moreover, when you don't have an anthracycline on board as you can see here, seems to be milder and more readily reversible. I think because of the toxicity concerns, nonanthracycline-based regimens have become very popular in this country, although both anthracycline and non anthracycline-based regimens are certainly acceptable. So the cardiac toxicity is less common if we can avoid anthracyclines. In many cases, it is reversible and in high-risk disease, it's the kind of thing that we may treat through, give a treatment hold, and continue treatment according to the guidelines. So the duration of trastuzumab that was used in the United States and in the first European trial was a year. It was picked out of the air and it's often said that the number—the length of time it takes the earth to travel around the sun really

should have nothing to do with how long we give trastuzumab, but that's what was done and it turned out to be a pretty good guess. There were a couple of trials that I'll talk about now. The HERA trial, this European trial, which looked at sequential treatment and looked at chemotherapy or chemotherapy followed by trastuzumab for a year or two years. Here you can see the trial design; patients had got chemotherapy, either neoadjuvant or adjuvant chemotherapy, largely anthracycline-based chemotherapy, and then were observed or got trastuzumab for 1 or 2 years. And 1 year was beneficial, just as in the US trials. Here you see 2 years versus 1 year, and you can see there's no difference between those curves. Two years of trastuzumab did not seem any better than one year. So it looked like 1 year was—there's no reason to go any longer than that with trastuzumab. And there was a reason not to that you see here; there was increased cardiac toxicity. A lot of times we think about the cardiac toxicity as occurring early, but here in the 2-year arm, they continued to develop cardiac toxicity during that second year, so again, 1 year of trastuzumab both for safety and efficacy seemed to be the right length. And what about a shorter duration? You may be familiar; there was this FinHer trial that was done that gave just nine weeks of trastuzumab. It was a very small trial, and it looked like they were seeing a magnitude of benefit that was similar to what was seen in these other trials, so maybe we can give it shorter than a year.

This is one of several trials that was done looking at this. Now the study design you see here, they go chemotherapy and trastuzumab for 6 months and then were randomized to continue to a year or to stop. This was designed as a

so-called noninferiority randomized trial, and unless there are some statisticians out there, this was a very confusing kind of trial design and I'll try to clarify it a little bit to the best of my ability. What they originally designed it to look at, so the 6 months would be considered noninferior if it was equivalent or even 15% worse than a year of trastuzumab. The trial design was this, and to help you interpret this, I'll show you this slide. This shows the relative risk here, and if the experimental arm is all here, the median and the 95% confidence intervals are all better than the control, then it's superior, and if it's worse than the control, it's inferior, and if it's in this range where it's kind of bridging the 95% confidence intervals goes into this indeterminate range, its considered noninferior. This is this 15% worse. If this 95% confidence interval spreads into this part where it might be inferior, it's considered indeterminate and in this trial 6 months versus a year this is what was found, this was indeterminate so that they couldn't say the 6 months was noninferior to a year. It was not better, not worse, but not noninferior. It's all very confusing, and the bottom line is it didn't prove that it was noninferior. So a year continued to be the standard.

There are other trials looking at this. This short HER trial actually looked at, again, just a short duration of treatment with 9 weeks, and this also gave an indeterminate result. This was just presented at ASCO this year; there are other trials looking at this. While there's not a huge difference between a year and shorter durations, we can't yet say that shorter durations are noninferior. So that 12 months of trastuzumab remains the standard of care right now, but I think we can tell our patients if they have to stop early because of side effects or some

other reason that they have gotten some benefit from the treatment even if it's just for a few months. The other issue we have is what I call adjuvant trastuzumab limbo: how low should be go? The original trials I showed you were largely node-positive patients, and now that we know the treatment works, we know some of these node-negative patients also have a risk of recurrence as high as 20% even for stage I cancers, higher than anybody would like, can we apply this treatment to them? And so this trial was done and it's a nonrandomized trial presented and published in the *New England Journal of Medicine*. Patients with tumors who were node-negative, they allowed micrometastases, although they only had a few such patients on it, in tumors less than 3 cm were randomized or not randomized, were just assigned to get treatment with paclitaxel plus a year of trastuzumab with paclitaxel given weekly. Here you can see the patient population. You can see most of the patients were in this range of 0 to or you know stage IA, IB, IC tumors—a lot of smallish tumors that you see every day nowadays. And here are the results. No matter what you look at for an endpoint, disease-free survival, recurrence-free survival, and so on, it made no difference, outcome was excellent, so these patients do very well with this regimen, all of them. The results are in the high 90s. Weekly paclitaxel with trastuzumab produces excellent outcomes in patients who are node-negative with tumors less than 3 cm in size.

Now with trastuzumab coming into the adjuvant setting and being very firmly established, of course, there was a need for other drugs first in the metastatic setting and then advancing them into the adjuvant setting. And we

have a few such trials. Pertuzumab is one such drug. I think you are all familiar with this agent in the metastatic setting where prolonged survival when added to trastuzumab and to taxane. Pertuzumab is another monoclonal antibody like trastuzumab. This cartoon shows mechanisms of action. Trastuzumab binds to those millions of HER2 molecules and is internalized into the cell and disrupts the signaling, so it disrupts the intracellular signaling the Wendy showed you and it may also induce antibody dependent cellular cytotoxicity, so an immune response. It's a little bit controversial, but there is some evidence of that. Pertuzumab by itself doesn't do too much, but it does seem to add to the effectiveness of trastuzumab. It binds to a different portion of the molecule, it binds and here inhibits the binding heterodimerization of the HER2 with other HER family members. Remember that HER2 is a member of a family, it can homodimerize with itself and induce signaling, or it can heterodimerize with other molecules of this HER family and induce signaling. And the particular HER2 and HER3 interaction is inhibited by pertuzumab and pertuzumab as I said did improve survival in patients with metastatic disease and in the neoadjuvant studies, so in which patients got chemotherapy prior to surgery. I'll point out these two arms. This is just docetaxel and trastuzumab given prior to surgery in patients with fairly large breast tumors, and 25% of them had pathologic complete responses, no tumor left at the time of surgery, so very encouraging results, but obviously most of the patients still had residual disease. Adding pertuzumab increased that to almost 46%, and then subsequent trials looking at this combination of docetaxel, carboplatin, trastuzumab, and adding pertuzumab

to that as in the TRYPHAENA trial. Probably what a lot of you have seen in your practices is that patients, about 50% or even a little bit more of patients will have no tumor left at the time of surgery, so there was a lot of excitement about this.

Looking at patients who do achieve this pathologic complete response as you can see here, they do much better than the patients who don't achieve a pathologic complete response. Adding the pertuzumab improved the pathologic complete response rate to 50% or even a little bit more, and those patients did much better than patients who had lesser degrees of response. So it's kind of a slam dunk to think that adding pertuzumab to chemotherapy with trastuzumab would produce improved outcomes. This trial was done, the so-called APHINITY trial, and it was just recently presented and published, in which patients who were HER2-positive were randomized to chemotherapy, trastuzumab and placebo, or chemotherapy, trastuzumab, and pertuzumab. The inclusion criteria and exclusion criteria you see here; this was a very broad range of tumors. You can see that no negative disease was allowed into this so that we would know how low we could go, how low we could extrapolate any results. A very large trial, but these are the results, extremely disappointing, I would say. They were statistically significant as you can see here, but there's very little difference between those curves. The pertuzumab added relatively little as you can see here, just less than 2% difference. Now the good news was the patients did better than anticipated, they were expecting the 89.2% to be disease free at 36 months versus the 93.2% that was observed, but this was statistically significant, but clinically modest, and so the number needed to treat to prevent an invasive

recurrence was 112. They had to treat 112 women to prevent one invasive recurrence, and if you were that one patient, then certainly it's worth it, but looking to the cost to society if you say pertuzumab costs roughly $100,000.00 for a year, you are looking at over 11 million dollars to prevent a recurrence. And this is the kind of thing that our healthcare system is going to have trouble accommodating.

So what's the role of pertuzumab now in adjuvant therapy? We are still waiting for some final adjudication on this. We can say it's not justified in these patients who are node-negative, especially those with smaller tumors, those who are ER-positive—so node-negative ER-positive disease I would say there's no reason to do it. Patients with these tumors smaller than 3 cm and node-negative, they do very well with simple chemotherapy and trastuzumab. In the higher-risk patients, those who are ER-negative, node-positive, the benefit from this is a little bit more, and those are the patients we might consider it in. But in-between, I think your guess is as good as mine, and it also raises questions on what is the role of preoperative therapy in this group of patients. Everybody has been very excited about it, but it really didn't predict the magnitude of benefit that was seen in the adjuvant setting. So we are all kind of rethinking in whom we really need to do preoperative therapy, and this is the kind of thing perhaps we can discuss in the question-and-answer session. We have looked at shorter durations of treatment, longer durations of trastuzumab, adding different agents to it. I should add lapatinib with similar results, it showed encouraging neoadjuvant results, but it did not translate into better adjuvant therapy. The new kid on the block, if you

will is this one, neratinib, which was just recently approved for extended adjuvant therapy as Wendy told you. This is treatment after you have completed a year of trastuzumab. Now what is neratinib? It's an oral tyrosine kinase inhibitor; it's different than months of the others that are available or being studies now in that it's, one, irreversible, and that in addition to targeting HER1 and HER2, it also targets HER4. Toxicity we'll discuss; 240 mg a day was the dose that was elected to be studied. It was looked at in metastatic disease, but also in this extended adjuvant setting, so this is the so-called ExteNET trial: neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer. A very large phase III trial, and this is the trial design. Patients completing chemotherapy and a year of trastuzumab, and if they were within 2 years of completing trastuzumab, they could go on the trial and they got either placebo or a year of neratinib. This is just to show you it's a very large trial, over 3,000 patients, 2,800 some who finally were randomized and able to be analyzed and here are the results. And you can see that these patients did well, but the patients who took neratinib in blue did a little bit better and you saw those figures early on, so that based on this you reduce the rate of recurrence by about a third, so it was statistically significant as you can see there . Here I'll show you the numbers. In terms of invasive disease-free survival, 90.2% of neratinib patients versus 87.7% for the placebo patients disease-free survival counting DCIS 89.7 versus 86.8. Time to distant recurrence 91.8 versus 90.3, and those were all of great interest, the top two statistically significant. CNS recurrence was numerically less; this was not statistically significant. This is of interest because

neratinib seems to have some activity in CNS metastasis, but fortunately although it's all too common, it was not very common in this trial in either arm. Here you can see the results by subset, so everything to the left is where the neratinib group was better, and these are various subsets. There was a particular advantage in the hormone receptor–positive patients that you see here.

We are still trying to explain this, but I think there are two explanations; one is that difference in natural history that I showed you earlier that the hormone receptor–positive HER2-positive patients are more likely to have these later recurrences than the hormone receptor–negative HER2-positive patients, and then also the fact that you're giving concurrent hormonal therapy and trastuzumab as Wendy showed you. This counteracts some of the mechanisms of endocrine resistance, and just like it's better to give chemotherapy concurrently with trastuzumab, it's better to give the neratinib concurrently with the endocrine treatment in these patients. It seemed to be the hormone receptor–positive patients seemed to benefit particularly, and in the node-positive patients, the proportional benefit was about the same, but of course their overall risk was higher, so the absolute difference would be larger. Here you see the side effects and the principle one is this, diarrhea. At the time this trial was done, we weren't really that familiar with how to manage the diarrhea. I'll have to confess we did phase I trials with neratinib back when it was just being developed, and the diarrhea was a real problem, we actually were able to go higher than this dose, but it was a steep learning curve for us to learn how to take care of it. Wendy's going to tell you about a trial that has nailed down the best way to manage these

patients, and it should be very familiar to anyone who wants to use this drug in this extended adjuvant setting. But you can see at the time this trial was done, 40% of patients had grade 3 diarrhea when they got neratinib as compared to 2% of the placebo patients. The diarrhea is worse at the beginning, it does get better, so you really have to learn to control it at the beginning and get the patient through it so they can enjoy the benefit of getting this treatment.

So to summarize some of these early trials, I showed you the B-31, the HERA trial, the BCIRG-006 trials that showed either anthracycline or nonanthracycline-based chemotherapy with trastuzumab was better than chemotherapy alone, that 2 years was no better than 1 year, and the NOAH trial looked at neoadjuvant trials and as did the GeparQuattro and other studies that showed this could produce pathological complete responses. The FinHer trial and PHARE trial looked at shorter durations of treatment, and although there is efficacy, it's not as efficacious as the year or at least it couldn't be proven out to be noninferior to a year. The ALTTO and TEACH trials were interesting, but negative. They were performed with lapatinib. The TEACH trial was actually the first extended adjuvant therapy trial, but that was negative and it was open to patients who never had had trastuzumab and who had received standard chemotherapy and were out a couple of years and were randomized to be lapatinib or not, and they did not benefit. Then I showed you these other trials with newer agents, the NeoSphere, TRYPHAENA, and APHINITY with adding to trastuzumab pertuzumab. Now the KATHERINE and KRISTINE trials are looking at ado-trastuzumab emtansine or TDM1 either in the adjuvant or neoadjuvant

settings. I should say the KRISTINE trial looked at TDM1 with pertuzumab versus this kind of TCHP: docetaxel, carboplatin, trastuzumab, and pertuzumab. So TCHP, what probably most of you have used in the neoadjuvant setting, versus TDM1 plus pertuzumab, and the TCHP was better, although it was more toxic. MA.17R was the first extended adjuvant trial and that was with hormonal therapy alone with letrozole. What can we say, again, summarizing: the NeoSphere 5-year data shows the neoadjuvant pertuzumab is beneficial when combined with trastuzumab and docetaxel with early-stage breast cancer, beneficial in terms of pathologic complete response rate.

For neoadjuvant treatment chemotherapy, trastuzumab, pertuzumab with a taxane-based regimen can be recommended because that gives the highest pathologic complete response rate. Looking at breast cancer recurrence after 5 years of endocrine treatment recurrence continues, 5 to 14, at least to year 20. So there's this continued pressure to recur for ER-positive breast cancer, and this is true in the HER2-positive, ER-positive as well as the HER2-negative, ER-positive. Adding trastuzumab to paclitaxel after AC in early breast cancer gave a sustained reduction in recurrence, but 2 years was no better than 1 year.

So what about future treatment options? The KATHERINE trial looks at trastuzumab emtansine versus trastuzumab as adjuvant therapy in patients who have residual disease after neoadjuvant chemotherapy. We had this trial open and patients got neoadjuvant chemotherapy, which could continue pertuzumab, and if they had residual disease, then they were randomized to continue trastuzumab to complete a year or to get ado-trastuzumab emtansine. We don't

know the results of that trial. KAITLYN was a similar concept in the adjuvant setting. I've talked about some of the drugs that we are giving, and this new drug, neratinib, with its unique toxicity. Now Wendy is going to tell us about selective symptom management of HER2 therapeutic agents.

MS. VOGEL We're going to focus on two toxicities tonight: cardiotoxicity and diarrhea. We'll start with cardiotoxicity, and this is usually an asymptomatic decrease in left ventricular ejection fraction, rare clinic heart failure, type 2 cardiac dysfunction. What this really represents is a loss of contractility. It's less likely to be associated with myocyte death or clinical heart failure, and it doesn't appear to be related to cumulative dose. It is generally reversible with treatment discontinuation, and we can certainly rechallenge after recovery. There are some risk factors for cardiotoxicity, however, previous chemotherapy particularly with anthracyclines. We saw some data that Dr. Budd presented from the clinical trials that certainly confirm this. Concurrent treatment with anthracyclines—we quickly learned early on that that should be a no-no. Pre-existing heart disease, age greater than 50, and obesity. What was very interesting that came out of this that was not considered a risk factor was concurrent treatment with radiation therapy. So how do we monitor cardiotoxicity? Obviously baseline and serial assessments of left ventricular ejection fraction is a must. If we have a normal baseline then we will proceed with therapy. If we have an LVEF of 40 to 50% with risk factors, then we may need to evaluate the risk/benefit and then proceed, but obviously watching that patient very carefully.

During therapy, we'll need to monitor for signs and symptoms of heart failure, and this could include an increased heart rate, perhaps swelling and increase in weight, S3 gallop upon exam, new dyspnea on exertion. We may see elevated jugular venous pressure, we may see sinus tach, tachypnea and crackles. Optimum surveillance is not well defined. Generally we do what was done in the clinical trials, so generally we are looking at 3, 6, 9, and 12 months evaluation while on therapy and certainly any time symptoms of heart failure appear. So how do we manage this? The best thing to remember is look at your prescribing information, and this information is taken right out of that. For trastuzumab, if we have an LVEF decrease of 16% or more from baseline or 10 to 15% from baseline to below the lower limit of normal, we will hold trastuzumab for four weeks and then reassess. If we have not recovered our LVEF, then we will need to discontinue trastuzumab, and if symptomatic heart failure occurs during treatment then trastuzumab should be discontinued. For lapatinib, for LVEF decreased to less than 50%, LVEF decreased to institution lower limits of normal, and if development of clinical heart failure, then we would want to hold lapatinib.

A dose reduction is recommended if LVEF recovers to normal after a minimum of 2 weeks and the patient is asymptomatic. For ado-trastuzumab emtansine, then if LVEF falls to less than 40% or is 40 to 45% with greater than or equal to 10% of absolute decrease below treatment value, we will need to hold the drug. For pertuzumab, assess LVEF every 2 months in the metastatic setting and every 6 weeks in the neoadjuvant setting. That gives us a little more

guidelines for this drug in terms of how often we would monitor them. For LVEF, if this is less than 45% or 45 to 49% with greater than 10% absolute decrease below baseline, we will need to hold pertuzumab and trastuzumab. We'll repeat at that point LVEF assessment in 3 weeks, and we would discontinue trastuzumab and pertuzumab if LVEF has not improved or declined further unless the benefits for the individual outweigh the risks. So how do we manage this medically? This is going to be our standard medical management, which may include beta blockers or ACE inhibitors.

Let's talk about diarrhea. Only advance practitioners can talk about diarrhea over dinner, right? I used to travel with my daughter and I'll never forget, she was probably about 14 at the time and I was talking about diarrhea and she begged me, "Mom, please don't tell anybody what you're talking about." And you know when you travel on a plane too and you know you are sitting next to someone and they're like, "Oh you're a speaker, what are you going to talk about?" "I'm going to talk about diarrhea." No more conversation. You don't have to worry about a chatty seat mate. So let's talk about diarrhea with HER2 therapy. As we've seen in some of the clinical trials that we've looked at tonight, diarrhea is one of the most common side effects of HER2 therapy. We have an increased incidence with lapatinib, pertuzumab, and neratinib. This is because of EGFR HER2 dual inhibitors, and neratinib can be responsible for grade 3 diarrhea. Diarrhea can occur in up to 95% of patients on HER2 therapy, and the incidence does vary between the agents. What we see here is a disruption of the

heterodimerization between HER2 and EGFR, HER3 and HER4. Risk may increase also with concomitant chemotherapy.

So what happens when you get diarrhea? You know diarrhea is not diarrhea is not diarrhea, right? So we can get dose delays, we can have patients die from diarrhea, we can get dose reduction, we certainly increase our cost of care, patient quality of life absolutely goes down, these patients know where every bathroom in town is and certainly we can certainly have reduced treatment adherence. What are some predictive factors for grade 2 or higher diarrhea? Actually age is one. There is a 3% increase per year in age for diarrhea. If they have had grade 1 diarrhea in a prior cycle, we have a twofold increased risk. And this is really interesting, if you start the therapy in the spring, we have twofold increased risk. How are we going to manage this diarrhea in our extended adjuvant setting? We are going to look at a trial called the CONTROL trial. This was published in abstract form this year, 2017, and this was a phase II trial of neratinib with loperamide prophylaxis in HER2 early breast cancer after adjuvant trastuzumab. This gives you a pretty picture of the abstract, and then we are going to pick little pieces out of this abstract and look at it now. This was the CONTROL study design. This was actually designed to characterize the incidence and severity of diarrhea in patients with HER2 early breast cancer who were treated with neratinib and loperamide prophylaxis. Early HER2 breast cancer, and they received up to 1 year of adjuvant trastuzumab, the stages of disease were I to IIIC, and they could have been hormone receptor ER/PR positive or negative. The dosing of neratinib is 240 mg a day. If they were

appropriate for endocrine therapy, they would also look at that. This was a year of therapy. Diarrhea prophylaxis, we are going to look at in a moment, and we are comparing this to diarrhea prophylaxis given on an as needed versus scheduled therapy.

Study objectives were to look at the incidence and severity of diarrhea, and we also wanted to see if there was any association between loperamide exposure and incidence of severity, we wanted to look at the incidence of SAEs (serious adverse events) and look at patient-reported health outcomes as well. Here is the loperamide schedule. The original dosing protocol looked at loperamide 16 mg, which was a 4 mg plus a 2 mg dose given every four hours on day one, loperamide 12 mg a day, which is 2 mg every four hours on days two and three, loperamide 6 to 8 mg, which was a 2 mg dose given every six or eight hours on days four to 56, and then from day 57 onward PRN dosing. Now then there was an amendment dosing that came along, and the amendment dosing changed this a little bit. The loperamide was then given at 16 mg, which is 4+4 mg dose, but given TID on day one, then from days two to 14 loperamide 12 mg a day and days 15 to 56 8 mg a day, and then again from 57 onward PRN. Later on, two cohorts were also added with a combination of loperamide and budesonide, and budesonide is a locally acting corticosteroid that we believe to target the inflammation that's associated with neratinib-induced diarrhea in a preclinical model, and the dosing was 9 mg a day. These are extended release tablets and this was given for the first cycle. The next cohort that's added and this is still going to be a stay-tuned message is the combination of loperamide

plus colestipol, and this is a sequestrant believed to target the bile and malabsorption also seen in preclinical models of neratinib-induced diarrhea. This was also given for the first cycle.

This is part of the message here that shows you the cohorts as they were added and in planned enrollment. You can see that we have added the last two cohorts in 2017. When we are looking at neratinib, and we are also comparing the data in the CONTROL trial to the ExteNET trial that Dr. Budd was telling us about earlier, we saw that most of the events for this treatment-emergent diarrhea were during the first treatment cycle, so that kind of tells you why the dosing of loperamide was different for that first 56 days and why things were done. Loperamide prophylaxis was given for two cycles. Seventy-five percent of all diarrhea events occur within that first 4 weeks of treatment, and over half of all grade 3 events occurred during the first week, so you can see how education is going to be so, so important in making sure the patient doesn't read the box of the loperamide, right, "I don't know how many to take," that we absolutely emphasize to them on how to take their loperamide. No grade 3 events occurred after the first cycle and no grade 4 diarrhea observed as well. This just gives you an idea. I've kind of broken this into two slides because it was a little difficult to read close up, but I will show you that if you look at any Just look at diarrhea percent, any grade; you'll see in the original dosing schedule it was 82%. If you look over a little bit more when we have the modified schedule, it's 73.8%, and this is all grades of diarrhea. When we add a corticosteroid, you can see that now are dropping down to 65 and we are comparing this with ExteNET trial, which

was loperamide dosing on a PRN basis, and we had all grades diarrhea of 95%, so very different when we start paying attention and looking at scheduled dosing. This, again, compares to grade 3 or any grade diarrhea, so if you look and specifically look on this slide at grade 3 diarrhea, you can see differences there compared to the neratinib arm with loperamide only given on a PRN basis. This is an interesting beautiful picturesque trial, but what I want to point out to you if we look at this on the far left of the screen, you can see that the tallest column, if you will, was ExteNET when we are only looking a loperamide given on a PRN basis. The second column is the control trial looking at loperamide prophylaxis given on a scheduled dose, and then the control trial then is the third column, which looks at loperamide prophylaxis with the addition of corticosteroid. So you can see here we've got a nice decrease in that column when we've given loperamide on a scheduled basis in higher doses and the addition of corticosteroid. When we add colestipol, that's going to be another column that will be added when those results are available. So conclusions. A structured loperamide prophylaxis regimen for two cycles significantly reduces the incidence, the severity and duration of neratinib-associated diarrhea when we compare that to events observed in the ExteNET trial. Preliminary data suggests that adding budesonide to loperamide prophylaxis may further diminish the duration and number of episodes of diarrhea as well as decrease the number of neratinib dose holds, dose reductions, and dose continuations. We also saw that ExteNET demonstrated that diarrhea was most often characterized by high-grade diarrhea, up to grade 3 diarrhea, it was highest in the first month, and it was

persistent in a large proportion of patients in months 2 to 12. When we looked at the CONTROL study, we saw that diarrhea was characterized by a lower percentage of high-grade diarrhea in month 1 and a much lower incidence in months 2 through 12. The adaptation to the effects of neratinib are observed noticing that higher-grade diarrhea occurs early and does not typically recur. So by controlling these early diarrheal events, we now understand that loperamide prophylaxis may help to improve long-term adherence and certainly ensure that we get those efficacy results by being able to give that dose on time and timely in complete dosing. We know that adding budesonide also this cohort is an ongoing cohort, it's still a stay-tuned message if you will; it's looking very, very good, and we will look at the testing of additional investigational agents as we noted in those additional cohorts.

The final analysis of the CONTROL study will be performed when all the patients on this trial have completed 12 months of neratinib therapy. What is the role of the advanced practitioner in caring for patients who are undergoing HER2 breast cancer therapy? Certainly we have a role in patient selection. When we talk about different treatment options that we have and we saw all of these different trials, assimilating this data for our patients can be a very hard thing for our patients to understand, so helping them become informed about their care and picking the appropriate patient for the appropriate therapy is very important. It is essential that we do baseline assessments, not only of the extent of disease, but also cardiovascular history; we may also look at GI history, and pick the appropriate patient for the appropriate treatment. Patient education is key, not

only about their disease process and the treatment that we give them, but self-management of potential toxicities, being proactive and not reactive to toxicities. They need to know when to report toxicities and to whom, and certainly teaching our nurses, our triage nurses, on what's going on with this patient that this just not is diarrhea, "Take two loperamide and call me in the morning" kind of thing that we need to be very alert of this in educating our staff. Monitoring tolerance to treatment is also very important. In Tennessee, we say we want to ride that horse just as long as we can, and that means we want to keep a patient on a good therapy as long as we can, and that means managing tolerance to treatment. Grading of toxicities is very important, overseeing triage calls, we know that this is different from chemotherapy-induced diarrhea. We know that this will get better the longer they are able to stay on therapy, but we do know that we must maximally control this, especially during those first two cycles. We need to have a very high index of suspicion for problems—that means face-to-face assessments. A physical examination may be very, very important in these patients, and triaging them over the phone could be very difficult. This would include weight assessment, vital signs, and assessing for electrolyte abnormalities, and adherence is also really important both to our cancer therapy, but also to our toxicity management therapy as well. That's a definite problem with oral treatment. It presents a challenge, which is adherence. Studies have shown that adherence to oral agents as well as monitoring patients for side effects and being proactive in dosing and titration and psychosocial issues and monitoring for that as well definitely impacts clinical outcomes. I will put a little

plug in here that APSHO has developed an oral treatment adherence educational offering that will be available online, so do look for that, and that may be helpful to you and your patients and your clinical staff.

Another potential challenge of oral treatment is unique toxicities. The patients may not necessarily connect the toxicity that they have with their treatment because we all know that oral medications are much safer, right? And they have no toxicities, and you know many times our patients may actually believe that when compared to intravenous therapy. And we certainly know that that is not true. There also can be challenging dosing schedules. When we are telling our patients how to take this loperamide that certainly can be challenging and if they read the back of the box that says, “Don’t take over ‘X’ number of pills a day,” this could be a problem. We have a potential for drug-drug interactions and certainly drug food interactions as well. There are recognized barriers to adherence, our complex treatment regimens, if they are not adequately supervised, if they have poor communications with their healthcare provider, this has been seen to be a barrier to adherence. Also, if the patients are dissatisfied with their care. You wouldn’t imagine that your front staff could make a difference in adherence, but it may very well do that, and certainly inadequate social support.

Let’s look at a case study. So this case study is LM. I picked LM because my grandmother’s name was Lily Mae. and I thought that was very nice. LM is a 59-year-old postmenopausal woman. She palpates a mass in her right middle quadrant of her breast, and in terms of her patient history she is obese, she has

irritable bowel syndrome. In terms of medication history, she has hormone replacement therapy for about 10 years, which has been discontinued since her diagnosis of breast cancer. Surgical history: she had a cesarean section at age 28. Family history: father died of lung cancer. Now diagnostic workup: we have a diagnostic mammography and ultrasound. This reveals a 3 x 2 x 2.5 cm hypoechoic mass, three metastatic lymph nodes are also noted, and PET/CT is negative for distant metastases.

Core biopsy was performed, and we have an invasive ductal carcinoma grade 3, vascular invasion was not present; excisional biopsy of the single right axillary node is consistent with metastatic carcinoma. She is ER-positive and PR-positive. She has HER2 overexpression, which was done 3+ by immunohistochemistry, and she has a Ki-67 proliferative index of 20%. This makes her a clinical stage IIIA. So let's ask Dr. Budd, what would you do with this patient?

DR. BUDD This is a patient where we would consider neoadjuvant chemotherapy. This is a very large tumor, palpable nodes noted to be involved. We know this patient is going to require chemotherapy and trastuzumab. And since we know that's the case, the outcome is going to be no worse if we give neoadjuvantly. It does have certain advantages in terms of treating the tumor, maybe shrinking it away from the chest wall and make the surgeon's job easier. Going forward—I'm not saying it's standard of care now—but going forward, it may allow us to evaluate patients who need additional treatment in the future so that, for instance, this KATHERINE trial that was

mentioned, if it turns out that ado-trastuzumab emtansine is better in patients who have residual disease, then this neoadjuvant approach will have some advantages there, but even now I think this is a case where neoadjuvant chemotherapy would be a reasonable thing to do. Giving this TCHP regimen has probably, in an ER-positive patient, a little bit less of a 50% pathologic complete response rate.

MS. VOGEL Thank you. She does complete neoadjuvant chemotherapy and is followed by bilateral skin sparing mastectomies and sentinel node biopsy. Post-surgery, her stage is now ypT1a, pN0. Following recovery, LM continues to receive trastuzumab for a year. Tell us about extended adjuvant therapy in this patient.

DR. BUDD This is a patient who had high-risk disease. She is ER-positive, so this is a case where the extended adjuvant therapy with neratinib would be advisable. You can look at those curves; it's a few percent difference, and in the higher-risk patients, the absolute difference is going to be larger.

MS. VOGEL Thank you.

DR. BUDD Of course, it's important to give standard endocrine treatment as well.

MS. VOGEL Absolutely. Do you have any questions over this case discussion? Yes, ma'am? Oh, I forgot. We've got to have a microphone and we are also going to have some Q&A as well at the end, but if you have particular case questions. Right here, front row.

FEMALE Thank you. So for this patient in the case study, she has irritable bowel syndrome. Does that matter as far as neratinib? I mean should you be concerned about it. Would this be a good case to do budesonide, or should we just be doing only loperamide?

DR. BUDD You want to answer that?

MS. VOGEL Go ahead.

DR. BUDD The general philosophy that I have is figure out what the best treatment is for the patient and see if there's a way that that patient can get the best treatment. Try not to compromise the cancer treatment if we can. I would think about going ahead with treatment. I certainly would use the prophylactic regimen that Wendy described with loperamide, and the budesonide seems like a reasonable idea in this patient.

MS. VOGEL One thing also is you want to make sure that you know what her bowel regimen is before the treatment. You want a baseline of what her bowel movements are, how often she has them, characterizing that, so that you've got a baseline to compare it to when we go on with therapy. Great question.

DR. BUDD Good question.

MS. VOGEL Any other questions over this case study? All right. To summarize what we've talked about tonight: HER2 is overexpressed in 18 to 20% of all breast cancers. It's a more aggressive tumor type and associated with poor prognosis with a high rate or recurrence. HER2 testing should be performed on every breast cancer patient by IHC and/or FISH. HER2 pathway represents

opportunities to target drug therapy including trastuzumab, pertuzumab, lapatinib, and now neratinib. These agents can be given in the neoadjuvant, adjuvant, or extended adjuvant setting.

MS. VOGEL All right. Now we would like to be able to answer any questions that you might have. We have microphones that are going to be circulating. Please raise your hand and speak into the microphone if anyone has any questions for us tonight.

DR. BUDD Been a long day.

MS. VOGEL We did good. Do you have a question? Okay.

FEMALE I might have missed this in the talk, but is there any cardiac toxicity with neratinib?

DR. BUDD Cardiac toxicity?

FEMALE Yeah.

DR. BUDD No, there's not. You don't have to cardiac monitor these patients for cardiac toxicity. There does not seem to be a significant problem. There is hepatic toxicity, and you need to monitor liver function occasionally.

MS. VOGEL Good question. Other questions? We can't see you out there, we'll just tell you. Okay.

FEMALE How soon can we start the neratinib dosing after the trastuzumab?

DR. BUDD After trastuzumab, you could start it 3 or 4 weeks after. It shouldn't make a big difference. It seemed to be better starting it sooner rather than waiting 2 years.

MS. VOGEL Okay.

FEMALE At this point, with showing that it works with hormone responsive—how far back can I go looking at my HER2-positive patients who finished a year and were hormone responsive?

DR. BUDD Well, in the trial—I would say up to 2 years.

FEMALE Up to 2 years? Thank you.

MS. VOGEL Anybody else?

FEMALE We've actually had a couple of patients start the neratinib in our practice, and we have put them on the prophylactic dose of the loperamide and also given them prescriptions for Lomotil. And some of ours have still had significant diarrhea. Would you recommend on those patients to go ahead and start the budesonide on them?

MS. VOGEL I think that would be a very reasonable thing to do. Dr. Budd, would you also add more than that?

DR. BUDD Yes, I think so.

FEMALE Can you comment on where neratinib fits in the NCCN guidelines?

DR. BUDD I don't think it's been incorporated yet. It was just recently approved.

MS. VOGEL There's one.

FEMALE About a few weeks ago, I had a patient who came in and we wanted to place on neratinib. However, a week prior to, she was diagnosed with colitis and she was taking an antibiotic for that at that point. We talked to her about the neratinib and then we started talking about the diarrhea and things like that. She was concerned of course. At that point, we told her to hold on the neratinib until her colitis resolved. At what point in time would you say it would be good for her to start the neratinib? After the antibiotic, 2 weeks after, 3 weeks after? Should we start her on the neratinib with loperamide of course, but should we combine that with budesonide or should we just take it as a go?

DR. BUDD I guess I would wait for her to get back to her baseline in terms of her bowel function to as good as possible. In other words, if she's having a flare, wait for that to be completely over with before initiating treatment. And I should mention in these cases too, of course, it's important to work with her gastroenterologist.

MS. VOGEL There's certainly going to be a benefit/risk discussion with that patient as well.

DR. BUDD Okay.

MS. VOGEL I think we're good. No more questions? Thank you so much.

DR. BUDD Thank you very much.

MS. VOGEL Paige has some closing remarks if you'll wait one moment.

MS. GOFORTH If anybody has any questions or has a concern about that or you want to discuss that any further, there's some of the *JADPRO* people that are over there, so you can catch them as you go out the door. But this symposium has now officially ended. So don't forget to claim your credit and don't forget to complete your evaluations that are on the table, and if you didn't get those, again, just ask one of the *JADPRO* people at the door. I hope you have a wonderful evening, and we'll see you again in the morning.

[END]