OPERATOR: Greetings, ladies and gentlemen, and welcome to the mets medical update. At this time, all participants are in listen-only mode. A brief question-and-answer session will follow the formal presentation.

If anyone should require technical assistance during the conference, please press “star, zero” on your telephone keypad. As a reminder, this conference is being recorded.

It is now my pleasure to introduce your host, Janine Guglielmino. Ma’am, you may begin.

JANINE GUGLIELMINO, MA: Thank you, Kathleen, and welcome, everyone, to Living Beyond Breast Cancer’s annual two-part metastatic breast cancer teleconference series, “Living With Metastatic Breast Cancer: Medical Update.” We’re very proud, as always, to offer these teleconferences in October. Thanks to all of you who have taken time out of your busy days to join us, and to many others for today’s program.

I just want to introduce myself. I’m Janine Guglielmino, the director of publications and strategic initiatives at Living Beyond Breast Cancer, and I’ll be serving as today’s moderator.

Today’s program is designed to help you understand the latest research and emerging treatments in metastatic breast cancer. Because of new and more effective therapies, doctors are now able to treat some metastatic breast cancers as ... chronic diseases. Over time, you may undergo a series of different treatments to help control the disease, and help you live the best possible day-to-day life.

The information we’ll be offering during today’s teleconference can help you ask good questions of your doctors, make sound and confident treatment choices, and assist you in taking an active role in the ongoing management of your health and well-being. Today, you’ll learn about new medical treatments available, or soon to be available; what’s in the research pipeline and metastatic breast cancer clinical trials; and ways to talk with your healthcare team about what this research means today, and for the future for your care.

Today’s program, like all of our teleconferences, will be interactive. Following our presentation, we’ll take questions on the phone and ... online.

Living Beyond Breast Cancer would like to thank our sponsor today, Celgene, for their generous support of this teleconference series.

I just wanted to let you know about a few upcoming programs to take note of. On October 22, [2012], we’ll hold the second part of this teleconference series. That will cover the emotional impact of living with metastatic breast cancer ... today. We would love to see you there. On November 7, [2012] we’ll host a teleconference on nutrition, a very popular topic.

We’d also love for you to save the date for our annual metastatic breast cancer conference, which will be held this year in Philadelphia, the weekend of April 13 and 14, 2013. As always, we’ll be offering travel grants, so we encourage you to plan [ahead, and apply for a grant if you need one]. We hope to see you there.
A couple of housekeeping notes before we get started. If you need to leave the program early or you’re joining us late, we will post a podcast on lbbc.org ..., and we will post a transcript of the program at a later date. We encourage you to share the information with others who weren’t able to join us today.

One more piece of business before we get down to the program: The format, as with all of our teleconferences, will begin with a presentation by our speaker and then an opportunity for you to ask questions directly, either online or by phone. We’ll give instructions about how to ask questions right after the presentation.

I’d like to tell you a little bit about today’s featured speaker, Dr. Hope Rugo. Dr. Rugo is a clinical professor of medicine and director of the Breast Medical Oncology Clinical Trials Program in the division of hematology and oncology at the University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center. Working there, Dr. Rugo’s research interests include new therapies for metastatic breast cancer and supportive care. She is on our medical advisory board, and she has published many peer-reviewed papers and lectures — nationally, locally and internationally — on cancer-related topics.

Without further delay, I’m pleased to welcome Dr. Rugo.

HOPE S. RUGO, MD: Thank you very much, Janine. It’s a pleasure to be talking with you all today, even though I can’t see you. I was asked to speak about the treatment of metastatic breast cancer in 2012. What’s the hot news, essentially? I’m including a number of different areas. I will have an initial disclaimer, which is that I’m going to show you the data from these studies. Some of it is rather complex and may not be entirely clear. We have the question-and-answer period. I’m going to try to be very clear about specifics that might be useful for you, within the presentation.

What we’ll talk about today is, of course, what we have recently presented. [There is] ... at least one drug now FDA-approved in HER2-positive disease, where we seem to have great success in targeting the HER2 receptor and changing the outcome of this disease, both in the early-stage and metastatic setting. We haven’t had as much success in the treatment of triple-negative disease, mainly because we haven’t been able to find that single marker that unites all triple-negative disease. But we have learned recently that breast cancer is very heterogeneous. We may be able to develop targets by looking at groups of cancers. We’ll talk a little bit about that at the end.

Reversing hormone resistance has been an elusive goal for us. Eighty-percent of patients will have hormone-receptor positive, and a number of those will recur with metastatic disease. It’s very unclear why it is that cancers first respond to hormone therapy, and then don’t respond. They develop some resistance-mechanism. We’d like to be able to prevent that, or reverse it once it occurs. We have some new success in that area. Whenever we have a little bit of success, it stimulates a huge amount of research, so more money is put into that area — it is what it is. That’s sort of the nature of the beast. We’re excited about this initial step, the beginning of success.

Let’s talk about HER2-positive disease. This is a cancer which represents about 20 to 25 percent of breast cancers. If you develop metastatic breast cancer, there are initially very high response rates to chemotherapy in almost all [cases], but not [in] every case. Usually we give some HER2-directed therapy up-front. Trastuzumab, [brand name] Herceptin, would be the agent we would use up-front with chemotherapy. Then we had another agent, lapatinib, [brand name] Tykerb, that we were able to use in the second-line setting with the chemotherapy [agent] capecitabine, [brand name] Xeloda.

We have learned from a number of different trials, listed there at the bottom of the slide, that continuing HER2-directed therapy through progression seemed to improve response, and the duration that the cancer stayed [under] control. That’s important, because we don’t have any other situation where that’s the case. For example, once your cancer has grown while you’re receiving a specific chemotherapy or hormone agent, we don’t have any data to suggest that continuing it does you any good, even if you add another drug.
This is an antibody that works in a completely different mechanism. You may not actually develop resistance specifically to the antibody. Continuing it, or adding in another agent like Tykerb (or lapatinib), seems to be more effective than stopping all HER2-directed therapy.

We also did a study early in the days of Tykerb where we combined it with Herceptin — lapatinib and trastuzumab. That was better than giving Tykerb or lapatinib alone. We saw a survival benefit, actually, in that recently published trial. Clearly, this combined blockade of something that drives cancer growth is really important and effective.

The idea came up: if some cancers are going to be progressing with HER2-positive breast cancer — if they’re unlucky enough to recur — or we know that a percentage, maybe as much as 15 percent of HER2-positive disease actually presents with metastases. That means right when you first get diagnosed ... we want to be able to [do a better job of treating] those patients. We know ... HER2-positive disease is [relatively] unique in that there is a subset of patients who get their treatment, then stay on antibody therapy for [more than] a decade. As far as we know, some of those patients will actually be cured of their disease. ... Even if they aren’t [cured, they] are enjoying a very long survival compared to 1987, when we first learned about HER2 and understood that the median survival was two to three years, even from early-stage.

We also know that we cure many patients with early-stage HER2-positive breast cancer, adding trastuzumab (Herceptin) to chemotherapy, either before or after surgery and hormone therapy, as appropriate. I think we have a lot of really good background data ... [as we] move forward and ... [find out] whether or not some of our new treatments could change outcomes.

Pertuzumab is actually an antibody, like trastuzumab. But it binds to a different place on the HER2 receptor. I don’t think that you can see my arrow. I don’t know that there is a way to point. But if you look at the pertuzumab antibody here, you can see that it binds to a different place on the receptor, the HER2 receptor. The receptor is only active when it binds to another one in its family. Pertuzumab blocks the most active combination.

Interestingly, pertuzumab by itself is no Herceptin. Pertuzumab’s brand name is Perjeta. Herceptin works by itself in some patients with HER2-positive disease. But pertuzumab doesn’t. There’s something about this interaction and its effect that we don’t understand well. We do know that these antibodies have an effect on the immune system. That may be one of the most important ways ... these antibodies work, by flagging cells for destruction by the immune system, something called antibody-dependent cellular cytotoxicity ... [or ADCC].

Pertuzumab was very exciting. Actually there was a ... very exciting study that really heralded what we were going to see, which looked at patients whose cancers had progressed on Herceptin and chemotherapy. Either they got pertuzumab alone or they got trastuzumab and pertuzumab, so the two drugs versus the one drug. The patients who got the two drugs, about 30 percent, had a good response, which is really remarkable given the fact that their cancer was already growing.

Based on that exciting data, the CLEOPATRA study was designed. This was a phase III trial, so randomized, [with] a large number of patients. Patients [may] ... not have received any chemotherapy or HER2-directed therapy for their metastatic breast cancers, so newly diagnosed with metastatic breast cancer. They were randomized like the flip of a coin to receive either Taxotere — that’s docetaxel — at a slightly lower than previously used dose. Really important, because Taxotere, at the full dose, 100, is poorly tolerated. Then [in addition to docetaxel] they got either trastuzumab and pertuzumab, or [trastuzumab and] a placebo [instead of pertuzumab]. It’s placebo-controlled. The physicians and the patients would not know which agent they were on. The primary endpoint was progression-free survival assessed by a central group. They treated 808 patients. They confirmed the HER2 status by the central testing, which is really important.

It’s interesting that this group of patients was not heavily pre-treated. For example, if we did that [study] in the United States, at least 50 percent of our patients would have received prior Herceptin. But in this study, which was done internationally, only 10 percent [of participants previously received Herceptin]. About 50
percent of the patients had hormone-receptor positive breast cancer. But only a quarter received hormone therapy. It's a little bit different from the patient population we would see if we did this as a U.S.-only trial. Of course, we can't, because we don't accrue well enough for trials.

Here's the independently assessed progression-free survival. What this means is from the date of entry onto the study, [the question is posed]: how long does it take your cancer to progress? Now, you [may] ... not respond at all. Your cancer could not respond, and you’d still be included in this group. This doesn't look at response. It just looks at how long you go from treatment-start to progression. As you can see, it was increased 50 percent, so out to 18.5 months, which means that a fair number of patients who received the combination [are] way out here, two years out [and] still haven’t progressed. That's pretty amazing. If you follow this out, it’s a little more than 30 percent of patients, 35 percent. That's very exciting.

We look to the longer-term follow-up data from this study, because it was so impressive it led to rapid FDA approval in June of this year. The approval is limited to first-line therapy. If you’ve already gotten three lines of prior treatment, you really have to petition hard to get insurance to cover this. We haven’t been very successful, although it’s probably effective in much later-line therapy as well. There are a number of studies going on [that] will help us ... get approval once we see those results. The NCCN, our National Comprehensive Cancer Network, has recently come out with this year’s guidelines. They said that basically from NCCN’s guidelines, you could use this combination with any taxane.

You could use Taxol or Taxotere or Abraxane or whatever it is you are choosing.

One of the really important things in studies like this is to try to understand the impact on overall survival. This is an interim analysis, meaning that you don’t have the right number of events. By statistical planning, you needed to have 385 events — in other words, unfortunately, women who had died of their cancer. They predicted ... that would happen. But, in fact, it hasn’t. At 19 months they only have 165 events. That’s very good. It’s not great for making the final results of the study, but it’s really good for our goals, which means that women are living longer now than ever before with HER2-positive, metastatic breast cancer. So that’s exciting.

But what they showed here was a big difference in the number of events in the two arms, 69 versus 96, that suggests that the trastuzumab and pertuzumab combination is going to also improve survival, as trastuzumab or Herceptin first did when the data was initially presented and led to approval of this antibody. It’s really encouraging. It’s not yet definitive, because it’s too early. We probably won’t see data on this for some time, because patients continue to do very well. But it is very exciting information.

They did see that all the subsets of patients — you got chemo before, you didn’t; you got the Herceptin before, you didn’t — everybody seems to benefit. Most patients had some cancer left on scans after six cycles of Taxotere. Then they continued on Herceptin and Perjeta, the two-antibody combination. That’s very interesting. I think that suggests that you’re going to do very well, regardless of whether all your cancer melted away or not, if you just continue on the HER2-directed therapy.

Then pertuzumab or Perjeta added very little side effects — no additional cardiac, heart toxicity, and really just a little bit more decreased blood counts. It was just very well tolerated. This is practice-changing. I think it’s the new standard of care and very exciting ... to see this kind of improvement.

Just so that you can see the historical timeline of what these studies have shown, our first two trials, [by] Slamon [et. al.] and Marty [et. al.], the first trial led to approval of Herceptin, in combination with paclitaxel or Taxol. This second trial was done with Taxotere, the Marty trial, in Europe, much smaller. Then we have a trial, AVEREL, that looked at Avastin in combination with Herceptin and chemotherapy. I’ll talk about it in just a moment. Here’s the CLEOPATRA trial, the largest trial, again, the longest progression-free survival ... that we’ve ever seen in this disease — 18.5 months. We are really making progress.
Of course, I think our biggest interest now is trying to cure more women who have early-stage disease. The APHINITY adjuvant trial is ongoing internationally and is looking at basically standard chemotherapy for early-stage, HER2-positive disease with Herceptin and then either with pertuzumab or a placebo. That study actually has been enormously popular, as you can imagine. They believe that they will complete the accrual for the trial, which is of course the key to getting to the results, later next year. That’s very quick and exciting.

There’s one other HER2-targeted agent that’s very close to approval, so I thought I would talk about it here, because this is not in slide mode. … T-DM1 is actually Herceptin linked to a chemotherapy agent derivative of maytansine-1. That chemotherapy agent works in a way similar to a class of drugs called vinca alkaloids. They work by making the little proteins that allow cells to divide, clump up, and be ineffective. The cells can’t divide, and they die.

The whole idea with T-DM1 was this targeted delivery of chemotherapy agents. You can’t give maytansine by itself, because it’s too toxic. What you want is a drug that has a big bang for the buck. In other words, a small amount of the drug is very potent. What the T-DM1 does is … the Herceptin part binds to the HER2 receptor. The complex is pulled into the cell, and then it’s digested so that you release the toxin directly into the cancer cell, causing cell death.

We did actually two phase II trials looking at T-DM1 in patients whose cancers had progressed on Herceptin, and then the next one was on a bunch of chemo plus Tykerb, lapatinib. We saw 30 percent response rates, some very durable. I had three patients in my clinic who were on for — one for three and a half years before her cancer progressed, and the other two [patients] are still on therapy at more than three and a half years. [It’s] extremely well tolerated, every three-week infusion — no hair loss. The major side effects are actually low platelets and modest elevation in liver enzymes, mostly asymptomatic for patients.

The EMILIA trial was done based on the FDA saying they wouldn’t approve it [for] … compassionate use … after progression in HER2-positive disease. We compared T-DM1 to Xeloda, or capecitabine, and lapatinib, or Tykerb. This was a standard combination that had previously been approved, as I showed you in the very early slide. What they did was randomize almost 1,000 women, 980, in a one-to-one ratio. In other words, half got each treatment. Of course, you couldn’t placebo-control this.

You can see here that they did meet their endpoints. What this is, is, again, how long do patients go before their cancer starts to grow again? It’s really dramatically longer with T-DM1 than with Xeloda and Tykerb, 9.6 versus 6.4 months. [The terminology in clinical trials of] “events” usually means “what happened.” So “events in survival” means that somebody died. “Events in progression-free survival” [refers to] … how many patients [had cancer that] progressed. This is obviously what we call highly statistically significant. It’s supposed to be less than .05 in general, but the criteria were much stricter for this trial, and it did meet that criteria.

This is pretty dramatic. You can see that everybody responds right at the beginning, if you look at the beginning of these curves, where they overlap. Then they separate and they stay separated out. We’re out at two years. They’re still markedly separated. That’s very exciting.

Then, of course, one of the things we wanted to show in this trial — you’re going to use more expensive drugs. We keep adding new drugs, and increasing health care costs, and want to be quite sure. This is data presented just two weeks ago, less than two weeks ago, at the European Society for Medical Oncology meetings by Sunil Verma of Canada who published the data on the same day in the New England Journal of Medicine, showing that survival was also improved. The median survival was 25 versus 31 months. These are patients whose cancers have been already treated with Herceptin in the metastatic setting, and chemotherapy. Survival is markedly improved with this option. That was very exciting.

Then, when we looked at the adverse events, there was actually more diarrhea, serious diarrhea, and redness and blistering of the palms and soles on the hands and feet with capecitabine and lapatinib, or Xeloda and Tykerb,
as you would expect. For T-DM1, I mentioned the side effects. Thrombocytopenia is low platelets. The transaminitis is the liver enzymes.

But if you just look at — this is all-grade adverse events. They’re fairly similar. But if you go down to the serious adverse events — that’s something we grade as three or higher — there are more with the combination chemo than with T-DM1. More patients were able to stay on therapy. In other words, they didn’t stop treatment.

I think that this is very exciting. We want to always know that we’re not causing heart weakness. If you look at the bottom line of the table, you can see those are patients who had a drop in their heart function. It was equivalent between the two arms. Very exciting, and we expect to see T-DM1 approved for the treatment of metastatic, previously treated breast cancer in the near future.

There are a number of different trials going on. The MARIANNE trial, over 1,000 women, again, very similar to CLEOPATRA. It’s complicated, three different arms, but looking at whether T-DM1 and pertuzumab might be able to avoid any chemo, that’s just free. You wouldn’t lose your hair, and you’d be getting chemo and ideal antibodies, because if you’re giving TDM-1 and pertuzumab, you’re giving Herceptin, pertuzumab and those really potent microtubule inhibitors, a chemo drug. It will be interesting to see how that works. They’re comparing that, of course, to T-DM1 alone and then the standard, which would be Herceptin and a taxane, the standard before CLEOPATRA.

There are a lot of other studies going on … that will help us in terms of getting these drugs moving into the earlier-stage setting. This … is … a really neat trial. It’s started by Dana-Farber. It’s called the ATTEMPT trial. We have had a consortium where we’re all participating in these smaller adjuvant trials. This is looking to see whether or not T-DM1 could be the right adjuvant treatment for small HER2 positive cancers. We will randomize 500 patients who have stage 1, HER2 positive breast cancer to receive T-DM1, or to receive weekly Taxol for 12 weeks with a year of Herceptin, a previous regimen that we’ve used and have tested … and felt was really good.

I’m going to move on to Avastin … [which you know is] no longer approved for the treatment of metastatic breast cancer, based on concerns of the FDA about both toxicity and effectiveness. All of the trials with Avastin were positive. In other words, it all showed that Avastin prolonged the time to progression of disease. But based on toxicity from other diseases, not breast cancer, and also one trial looked great for breast cancer, and the other two trials didn’t look as great, mainly because they studied it in a different way that probably was a less effective way. … Looking back over it, it’s all clear what was done wrong. Nonetheless, we are where we are. One of the critical things is to find out which patients benefit from the addition of Avastin. I know this is an effective drug for breast cancer, but we need to figure out who is going to benefit the most.

Actually one of the markers that seems to be most encouraging, at the present time, is a blood-test called plasma VEGF-A. You have to collect the blood in a special way, so that it won’t make the blood clot. It looks, in the recent study AVEREL, which was again in HER2-positive disease, that patients — and I’m just going to explain it to you because I can’t point to the specific curves — but patients who had a high VEGF-A level had a worse outcome. If they got Avastin, their outcome improved a lot. Patients who have a low VEGF-A level didn’t seem to benefit from the addition of Avastin. There is some other data that supports this in other cancers, and in another study in breast cancer.

The problem is that these are all subsets. They didn’t require plasma to be submitted, so they only had it in less than 50 percent of patients. The numbers are quite small. If you look up to the top, where the little figure legend is, you can see it’s 45 and 37 and 36 and 43 — so really small numbers.

We have to prove that this actually would be useful. This confirmatory study is going on, to randomize patients to receive our standard chemotherapy before Avastin was
approved, the trial that actually led to the temporary approval, Taxol with Avastin or Taxol with placebo. They will look at VEGF high in all of the patients. Everybody will have blood tests. I think that this is a really, really important study, because I am hopeful that we will be able to salvage the good effects of Avastin.

As we move on to talk about hormone receptor-positive disease, this represents 80 percent of breast cancers that we see, and in fact is about 70 percent of the patients we see in the metastatic setting. It doesn’t mean that there’s a high rate of recurrence. It’s just a frequent cancer. Some cancers, of course, present with metastatic disease, unfortunately. We know that most of these cancers respond to hormone therapy, but develop resistance over time. We should be able to figure that out and reverse it. But it’s been very, very difficult to do that.

What we’ve done is use animal models without a lot of patient data from the tumors. Like we haven’t gotten a biopsy from your initial cancer, and then a bunch of biopsies from the metastatic cancer, to be able to compare what is actually going on inside the cancer. That’s one of the really important things we’re trying to do moving forward, so that we understand what kinds of things change that we could potentially target.

But we have made some — despite our lack of knowledge — we’ve made some improvements in the treatment of advanced ER, hormone receptor-positive breast cancer. This trial actually is now published in the *New England Journal of Medicine*. It’s one of our cooperative group trials that randomized women who had newly diagnosed, hormone receptor-positive metastatic breast cancer to receive Arimidex, or Arimidex plus Faslodex. What they showed, particularly in the group of patients who had never had any treatment — no prior tamoxifen, aromatase inhibitor, chemo, nothing — that progression-free survival, in other words, how long the disease is controlled before progressing, was longer in patients receiving the combination, as was overall survival. [That was] a surprising end point. In other words, women lived longer.

The thing that’s important to keep in mind here is that Faslodex was given, could be given to the patients who were given Arimidex up front. But Faslodex was approved during the time course of this study at half the dose that it is approved in now. Faslodex now is twice the dose and much more effective than it was. For some reason, they didn’t do their homework quite right and the drug was approved for seven years at a relatively ineffective dose compared to currently. We don’t really know that if the patients who were on Arimidex, who got full dose Faslodex afterwards, would have done as well.

What we’ve generally all taken home from this study is that if you have metastatic breast cancer, and never took any hormone therapy, it’s worth trying the combination. We use the higher-dose Faslodex in the combination. But otherwise I don’t use the combination in patients who’ve already seen hormone therapy. It is pretty well tolerated, but of course you get the injection [toxicities] as well as the oral drug’s toxicities.

One of the very exciting things we’ve seen recently is the data from targeting a particular pathway called the mTOR pathway, called mammalian target of rapamycin. It’s not a very nice name. We know that this particular pathway plays an important role in many different things that drive cancer growth. We’ve actually tried to target some of the things on the top — PI3-kinase, Akt and also the receptors. It turns out that there’s a lot of the ability to signal through other means. It overcomes the effect of that drug. The idea was maybe if you targeted something way down in the signaling pathway, you would be able to overcome all these other ways of activating PI3-kinase.

We actually looked at a drug called everolimus. The brand name of the drug is Afinitor. The first study that recently published was very exciting: I wrote an editorial on [it. A] randomized, small number of women — this is not the definitive type phase III trial. It’s only 110 patients — post-menopausal, progressing breast cancer, previously treated with either Femara (letrozole), or Arimidex (anastrozole), randomized in this phase II trial to receive tamoxifen, with or without Afinitor. The patients who took Afinitor had better control of their disease. Although they couldn’t really make a definitive comment about survival, they seemed to have lived longer.
We actually worked on first the trial showing that the combination shrunk cancers more in the neoadjuvant setting, and then this BOLERO-2 trial, which was published in the *New England Journal of Medicine* last December, and I recently updated for our ASCO breast symposium. Seven-hundred-twenty-four women were randomized, twice as many to Afinitor and Aromasin, or exemestane … [inaudible] receiving placebo and Aromasin. They had to have cancer that progressed on letrozole or anastrozole. That’s Femara and Arimidex.

What we showed was that the cancers were much better-controlled in patients receiving Afinitor. As you can see here, 3.2 versus 7.8 months. That’s [reported] by investigator. It was even longer [when reported] by the central review, very exciting data. We also showed that actually shrinkage of cancers — if you look at the clinical benefit here — was twice as frequent in patients receiving everolimus or Afinitor than in patients receiving the Aromasin alone.

… Everything comes with a cost. I mentioned pertuzumab doesn’t really seem to increase toxicity. T-DM1 is well tolerated. But everolimus or Afinitor actually does cause some potentially serious side effects that we have to know about: more mouth sores, more serious mouth sores. Then a very rare side effect [that] is seen is actually some fluid in the lungs, with the cough, and [there] can be significant shortness of breath.

What we found is that if we are aware of these side effects and treat them preventively, and watch for signs of … interstitial pneumonitis, [an inflammation] in the lungs, we can really keep most people on the treatments. Very few patients go off. For the mouth sores, we use a steroid mouthwash and we hold. If you get a mouth sore, reduce the dose. If you get the cough and we get a chest X-ray right away, and reduce the dose or hold. That seems to work very, very well. It’s not for everyone, obviously. We just have to test, and be aware of what kind of side effects occur.

The other thing we saw [that] was very interesting is that there were less — actually, the bones seemed to get a little stronger versus loss of bone in the patients receiving Aromasin alone. It looks like Afinitor actually blocked some of the bone loss and actually helped the bones … get a little stronger, based on markers that we got from the blood — very, very interesting.

Based on that, we wanted to … see whether or not there was a difference … in progression in bone. … If you had a bone metastasis at baseline, it looked like you had less progression, or it took longer to progress in bone. We also saw that [occur] … in patients in general, in the overall population. That’s a very intriguing endpoint, and it suggests that maybe there could be some benefits of this drug for early-stage breast cancer. Unfortunately, we still don’t know which patients’ cancers respond to everolimus (Afinitor). There’s a lot of work going on in that area, but [it] has not yet been fruitful.

There’s an early-stage breast cancer trial that’s approved by the National Cancer Institute [that] will open probably next year. That trial is looking at giving everolimus (Afinitor) or a placebo in patients who have high risk, early-stage breast cancer, who’ve completed their chemotherapy. They have to have hormone receptor-positive disease, and many positive nodes, or be at high risk. They’re going to get a year of everolimus as a single agent. … They’ll overlap with hormone therapy, but we don’t know that we’re selecting the right disease. We’re just selecting high risk disease. I think it’s an important study to do, and we’ll be able to look at the cancers as well by getting some tumor tissue from … [surgeries]. …

Just a little bit about new chemotherapy. We have a new drug, eribulin, which is approved for later in the course of advanced cancer. We’re doing a whole lot of different studies with eribulin, combining with different agents. I’ll show it to you in a moment. Eribulin’s major side effects are decreases in the blood counts. That can be quite severe, even leading to mouth sores. But dose reduction seems to work incredibly well, as do injection of the growth factors like Neupogen, to keep the white blood cell count strong. We’ve had really fabulous luck with this agent in many, many resistant cancers.

I presented at ASCO, [American Society of Clinical Oncology], the data from a randomized phase III trial
for advanced breast cancer, looking at three different agents with the idea of whether or not new agents would be better than the old agents, as first-line treatment for metastatic breast cancer. Patients received [the old agent,] Taxol [or one of the new agents,] Abraxane or Ixempra, three different drugs that work in similar ways but [the two new medicines] were thought to ... be better than [the older] Taxol. Turned out that some of it had to do with the doses that were given. People's tolerance was that Abraxane, although much more expensive, wasn't any better in this setting than Taxol. Ixempra was a little worse when given weekly. Ixempra is approved as every three-week dosing in the later-line setting, so that hasn't really changed. Abraxane ... is a good option in the first-line setting if you can't take the steroids, or [if you] have an allergic reaction to Taxol.

But it didn't result in better outcome in these patients. There were clearly more side effects when you pushed the dose up, with really serious peripheral neuropathy or pain and tingling in the fingertips and toes. ... These kinds of trials are really important in order to help patients know that the new thing is not always better, and that we have to be aware of potential side effects.

Where are we going? In HER2-positive disease, pertuzumab or Perjeta is the new standard of care for metastatic HER2-positive breast cancer, in the first-line setting. T-DM1, a very fascinating agent, was superior to our previous standard of Tykerb (lapatinib) and Xeloda (capecitabine). ... Many other combinations are being studied, including that drug Afinitor that I showed you in hormone-receptor positive disease.

I think it’s very exciting, [that] T-DM1 [is] available on compassionate use in some places. There’s also a compassionate use study open. I think that it will be likely to be approved by either the end of year, or maybe the beginning of next year, by the FDA.

For hormone-receptor-positive disease, the FDA approved the Afinitor/Aromasin combination, everolimus in patients progressing on either Arimidex or Femara. We have that earlier-stage study going on later this year, or early next year. Because there was success, as I mentioned, everybody and their brother, in terms of pharmaceutical companies, has new agents that are being studied. That’s great, because then there are a lot of resources in this.

One combination that we’re studying, which has been very effective, has been using the mTOR inhibitor, but with another antibody that blocks a receptor called the insulin-like grown factor receptor. We’re very excited about that trial, which we’re carrying out at our institution. Then there are a lot of other mTOR inhibitors that might have different toxicity, that would make them more tolerable. In this we need to really desperately find markers that predict response to specific treatments. We’re working on that.

We have some very exciting new data that came out. I just wanted to explain two different words. Genomic testing means looking at the DNA of a tumor, mostly. You could also look in normal cells, for example. You’re looking in normal cells for something you’re born with. Let’s say you’re screening for a BRCA mutation or something like that. If you want to look at the DNA of a tumor, of course, you have to have the tumor. Then you could look to see whether genes were deleted, or gotten rid of, or mutated — changes, or even amplified, like HER2, where you have too many copies of a gene.

For gene-expression testing, you’re looking at RNA. It’s a little more complicated. It’s taken a lot longer to get to where we are, because RNA is fleeting. DNA hangs around forever, like the dinosaurs. RNA is something that’s only made when you need it. What happens is DNA is made into RNA. An RNA piece is made. Then that turns into protein. A protein is a receptor or mTOR, or things like that. If you’re looking at RNA, that’s called gene-expression testing.

We have seen a really exciting new paper of analysis of breast cancer through The Cancer Genome Atlas network. It was all over the news. I’m sure you all saw it. It doesn’t have one author. It’s in the journal Nature. They identified — actually confirmed — what we’ve seen before, which is four main breast cancer classes. Then [they] identified some of the most common mutations. But what they really found was that breast cancer is very heterogeneous, that...
there were enormous variations within these main classes when they started to look at more details. They combined both the DNA and the RNA testing, as well as protein and additional factors. This was a very complicated analysis. I think that what it means is that we have to identify potential targets for individualized cancer therapy by sub-grouping the cancers even further. It’s likely that we’re going to need both combination tests, to predict response, and combinations of therapies outside of HER2 and the estrogen receptor.

... We’ve seen a lot about the PARP inhibitors, and we were disappointed with the results of the phase III trial that looked at a so-called PARP inhibitor chemotherapy, [that it] didn’t show a benefit. ... [When the company changed hands and more investigation was done], it turned out it didn’t really inhibit PARP. It does have some anti-tumor effects. But it seems as though we have to be a little smarter in how we’re using PARP.

One of the things that this paper [by] The Cancer Genome Atlas showed was that there was a subset of hormone receptor-negative, HER2 negative or triple-negative breast cancers where the genomic pattern looks very similar to serous carcinoma of the ovary. They almost look identical. That’s actually quite intriguing, because serous carcinoma of the ovary responds to PARP inhibitors with chemotherapy, whereas triple-negative breast cancer as a whole doesn’t. I think that moving forward we’re going to have to identify those patients whose cancers look like this, and then treat specific subsets differently.

That’s actually exciting. There are a number of PARP inhibitors in development. I think that this data published in Nature will help us study these particular agents.

Lastly, funded by Susan G. Komen for the Cure, we have a ... promise-grant based on work from my colleague, Lisa Coussens, [PhD], who’s now ... [at the] Oregon Health & Science [University], where she’s found that cancers ... [with] more of the immune cells called macrophages — [immune cells] — in them that that correlate with worse cancer, more tumor volume, faster growth, and more resistance to chemotherapy. The idea was that maybe patients would actually have a worse outcome, not just mice, if they had more of these [macrophage] cells in their cancer.

As you can see here, the bottom line, up in the basal box — basal being more of the hormone receptor-negative, HER2 negative cancers — CD68 is a macrophage marker, this immune cell. If you had a lot of macrophages and not very many of a T-cell called CD8, you seem to do worse than the reverse. In other words, worse survival. The patients died sooner from their disease.

We actually designed a study, which [just started] — and we’ve enrolled five patients — where we’re studying a drug that blocks the macrophages with eribulin, the new chemotherapy agent. We are doing biopsies of the tumor to better understand which patients will respond or not with fine-needle aspiration, so it’s not too toxic for the patient. Once we’ve determined the safe dose to combine, we’ll be doing a larger phase II trial with both Vanderbilt and Duke as partners. This is very exciting.

I just want to put in a plug for clinical trials. I think they’re incredibly important in terms of making decisions. I think that we have a lot of different ways of coming to consensus, and [answering the questions around] how ... you decide whether a clinical trial or a specific treatment is right for you. I think that we need to have consensus information that’s from many people working together, rather than one person’s opinion. ... As an individual patient, you need to have a very good communication pathway with your physician and providers. You need to be able to discuss options each time you go in, and talk about what the expected benefits are. That kind of open conversation is important. I think that you really need to be able to have your physician, for example, support a second opinion if you want to do that, look into clinical trials. ...

I wanted to highlight this Consensus Conference, which is in Lisbon, Portugal, the second one, in November of next year. This was a great conference the first year — it’s every other year — where 30 international breast cancer experts got together, and a lot of very good presentations, and then this consensus panel, where we voted on what should be the most important parts of care, and what are acceptable treatments for patients with advanced breast cancer.
Of course, even meeting every other year we can’t keep up with this rapid data, and drug approvals. But it’s a very exciting time, I think, where we’re making advances every day and understanding a little bit more about where to go in the future.

With that I’ll close. I’d be happy to take any questions you have.

OPERATOR: Thank you, doctor. At this time, we’ll be conducting a question-and-answer session. If you’d like to ask a question, please press “star, one” on your telephone keypad. A confirmation tone will indicate your line is in the question queue. You may press “star, two” if you’d like to remove your question from the queue. For participants using speaker equipment, it may be necessary to pick up your handset before pressing the star keys.

Again, ladies and gentlemen, if you do have a question or a comment, please press “star, one” on your telephone keypad at this time.

JANINE GUGLIELMINO, MA: Dr. Rugo, this is Janine. I’m going to start with an online question. This is a question that we get quite frequently. One of our listeners was curious about the validity and reliability of circulating tumor cell blood tests, particularly as a woman [who] is trying to make treatment decisions. [She wants to know] whether those tests can be helpful … [in] determining when treatment needs to change, and whether it’s working effectively for her.

HOPE S. RUGO, MD: You know we have data with — it’s a great question — with circulating tumor cells telling us if they don’t go down fast enough, or they’re not low enough, the outcome is worse overall. But we have no idea if that’s true for every individual patient. Some patients may respond more slowly. Also, we don’t have any data to suggest that if you change treatment based on CTCs and not based on the tumor itself, that you’re going to improve outcome.

I think the danger with using circulating tumor cells for a treatment of advanced breast cancer is that you might change treatment too frequently, and expose the patient to more toxicity than is worthwhile. I think in certain situations it might be useful, where there’s no disease to see. Some lobular cancers are hard to see. But otherwise I would be very cautious about using circulating tumor cells for a decision about treatment or not.

JANINE GUGLIELMINO, MA: Excellent. Thanks, Dr. Rugo.

OPERATOR: Thank you. Our first question is coming from [Pennsville, New Jersey]. … Your line is live.

WOMAN: Hi, doctor. Thank you so much. I appreciate this. I actually have a connected question. I’m taking Arimidex now, and the doctor wants to change my treatment because she feels the Arimidex is not working. But I noticed in your seminar that you said Arimidex and Faslodex together — she wants to change me to Faslodex by itself or change me to Femara. [I wanted to ask you if] … I could go on tamoxifen. Or … whether I should just add Faslodex to my Arimidex treatment.

HOPE S. RUGO, MD: Let me just answer that, quickly: … basically I don’t know what your treatment was before — if you ever got tamoxifen. It would be fine to use tamoxifen instead of Faslodex, and use Faslodex later.

WOMAN: Uh-huh.

HOPE S. RUGO, MD: The trial did not test the addition of Faslodex. It tested either up-front combination [or] … single agent. In this situation, you wouldn’t want to continue the Arimidex.

The Arimidex and Femara are very similar drugs. That’s not a great switch. Aromasin and everolimus is also an option. Aromasin and Afinitor is a trial that I talked about. But other than that, it’s hard to give an individual recommendation, just because I don’t know your case.

WOMAN: OK. That’s what I’m trying to work on now. I shouldn’t use Arimidex and Faslodex together. I can use Faslodex alone.
HOPE S. RUGO, MD: Yes.

WOMAN: Or I can use tamoxifen. Now, if I go on tamoxifen, should I also ask her to add the Afinitor to it? Or —

HOPE S. RUGO, MD: That you have to discuss with your oncologist. I think it’s beyond the scope of what I can answer here. I think that the approval is with Aromasin.

WOMAN: I lost you. The Aromasin approval for —

HOPE S. RUGO, MD: The approval of Afinitor in patients with hormone receptor-positive breast cancer is in combination with Aromasin or exemestane.

WOMAN: Oh, I see.

HOPE S. RUGO, MD: That is a good option for you. You can do that now. You could do that after Faslodex or tamoxifen.

WOMAN: OK.

JANINE GUGLIELMINO, MA: Thanks so much, Dr. Rugo. And thank you for your question.

[Operator], if you could go to the next question, please.

OPERATOR: Thank you. Our next question is coming from Rancho Mirage, California. Your line is live.

WOMAN: I have two quick questions. It’s been seven years since my brain mets.

HOPE S. RUGO, MD: Congratulations.

WOMAN: Thank you. Is there anything going on with studies along long-term effects from having brain mets?

HOPE S. RUGO, MD: Funny you should mention that. My colleague who shares the bar with me, Michelle Melisko, [MD], has looked at outcomes in patients with brain metastases, of course showing that survival is higher now than ever before, and also is conducting a study in HER2 positive disease, where we’re giving patients a new drug, neratinib, with Dana-Farber and our consortium of clinical trial sites. She’s looking at cognitive function in those patients. That’s the first study that I know of that’s really looking at … brain outcomes in patients who’ve had progressive brain metastases.

You have a fairly unique case, obviously, and I know you know that. Sometimes that’s true when we have effective systemic therapy and can completely resect a brain lesion, or something like that. I have another patient … who’s about five years out from a couple of Gamma Knife [radiosurgery] … treatments.

I think that we’re not going to know anything for you, because you defy all the data that exists. But I will congratulate you for that.

WOMAN: Well, thank you. My second question is: I’ve had a second cancer in my tongue. Does that prevent my participation in some clinical trials?

HOPE S. RUGO, MD: I don’t know, because I would need to know more about your cancer and what the outcome was. I think that if it’s a cancer of the tongue that can be easily resected — removed — and it has a very, very low risk, that then somebody can make a case of including you in a trial. But that, again, is going to be individually done.

WOMAN: OK. Thank you.

JANINE GUGLIELMINO, MA: Thank you, Dr. Rugo. And thanks so much.

Unfortunately, we are at the end of the teleconference. I know there are a number of you on the line and also online who had questions to ask. We would like to answer those questions online via our “Ask the Expert” this month [October, 2012], which also focuses on metastatic breast cancer. If you have a question, please go online to lbcc.org to our Ask the Expert section and ask your question [there]. … We’d be happy to answer it.

With that, I would like to once again thank Dr. Rugo for a really wonderful presentation that helped us understand
the recent research, and how things are moving forward. We’d also like to thank our sponsor, Celgene, for their generous support of this teleconference series.

I’d like to remind everyone … we will post a podcast and a transcript of this program on the website.

Finally — I neglected to mention this earlier — for those of you who seek peer emotional support at any time, we encourage you to call our [Survivors’] Helpline. That number is (888) 753-LBBC (5222). We have many women on our Helpline who are living with metastatic breast cancer and are here to talk with you about your issues and concerns.

Thank you so much, Dr. Rugo and [thank you to our operator], and I hope all of you have a good day.

HOPE S. RUGO, MD: Are we still there?

JANINE GUGLIELMINO, MA: We’re still here.

HOPE S. RUGO, MD: I just wanted to say thank you for your attention, [and] your excellent questions. Do send in your questions to the website.

Then to briefly clarify two things that were asked here that I thought — accessing T-DM1, go onto the [National Cancer Institute] clinical trials site because there are sites with compassionate use in this trial called TH3RESA. You can also call Genentech direct to ask by looking them up online. And then the chemo embolization is something that’s under … investigation, and we don’t really know. The rest of them I think are out of the scope.

I wanted to mention also about Abraxane or NA [neoadjuvant] paclitaxel. In my trial, the dose was 150 milligrams per meter, squared. That was too toxic. The standard dose for that drug is 100 milligrams per meter, squared. In that situation, I think it’s a very effective and useful drug.

Anyway, thank you very much.

JANINE GUGLIELMINO, MA: Thank you, Dr. Rugo.

[END OF TRANSCRIPT]