I am Adam Brofsky, MD, PhD, I’m Professor of Medicine at the University of Pittsburgh, I’m Associate Chief of Hematology Oncology and Associate Director for Clinical Investigation at the University of Pittsburgh Cancer Institute in Pittsburgh, Pennsylvania, and I’m going to today give you a pre-ASCO breast cancer update. I’m sure we’ll probably update this after ASCO in a couple of months, but for now I’d like to just talk a little bit about what I think at least in this slide shows are some of the hot questions, which are what’s the current state of the art of the use of Bevacizumab in metastatic breast cancer systemic therapy, are there any novel anti-Her2 new wave therapies that are ready for prime time? What about the novel therapies like PARP inhibitors in the treatment of triple negative breast cancer? And then finally talk a little bit about the role of bisphosphonates in the adjuvant therapy of breast cancer.

So the first question really is where are we with Bevacizumab in metastatic breast cancer? And again Bevacizumab is one of many agents that target the VEGF pathway, clearly the idea is to block the binding of VEGF to its receptor. And as you can see in this slide here, oh are actually we’re trying to see in this slide here, VEGF binds to its receptor, but if there are things that interrupt those pathway such as anti-VEGF antibodies like Bevacizumab, soluble VEGF receptors such as a VEGF trap, anti-VEGF receptor antibodies such as the M clone 1121b antibody, which is now actually in current development for metastatic breast cancer with a dose of Taxol, all of the – or small molecule VEGF inhibitors such as vatalanib, sunitinib and others, all of which kind of interfere with VEGF interacting with its receptor and as a result inhibiting survival proliferation and migration of endothelial cells and thereby inhibiting angiogenesis.
It turns out that this is a lot more complicated than people think, simply it’s just simply soaking up VEGF. There are a lot of other receptors actually that are involved in program cell death and proliferation of endothelial cells, there’s a whole angiogenin pathway that is now recently being exploited by a number of pharmaceutical companies, a receptor pathway called Ti-1 and Ti-2, which we won’t talk about today but there’s going to be a lot of interest in this in breast and other cancers that will be occurring in the next couple of months to years.

But what happens when we at least inhibit VEGF is the following. Initially there are the early effects, that is the tumor vasculature which is really twisted tends to normalize and that allows for increased blood flow into the tumor and actually increased delivery of cytotoxic chemotherapy and other therapies. That results in a higher response rate generally with antiangiogenic drugs, but the secondary and continued effects require continued application of Bevacizumab and that is that it prevents the blood vessels once they have been destroyed or once the tumor has been destroyed with its blood vessels it inhibits the, the growth of blood vessels into the tumor again. But that requires continued Bevacizumab exposure. If we stop exposing the cells to Bevacizumab or the tumor to Bevacizumab it can tend to regrow, and there is again a lot of interest in this both from the preclinical and clinical arenas both in breast and in other cancers.

So Bevacizumab, again, has a long history in breast cancer, the first trial was reported over 5 years ago, almost 6 years ago now. This is ECOG 2100 where patients with locally recurrent or metastatic
breast cancer were randomized to Paclitaxel with or without Bevacizumab and in this particular trial as you can in its most recent update about 3 years ago, the addition of Bevacizumab to Paclitaxel improved the progression free response rate for about 5.8 months to about 11.3 months, and that really didn’t matter whether it was an independent review or assessment by the investigators. The response rate also doubled in both cases from about low 20s to almost 50%.

So this is actually fairly dramatic and fairly encouraging, however, the one discouraging fact of this and a lot of other trials of Bevacizumab shows that there is only a 1.7 month difference in the median overall survival which was not statistically significant in this case, and so this has led to a lot of consternation, a lot of back and forth between the US FDA and the Roche Genentech, the pharmaceutical company that, that markets Bevacizumab and again the issue really becomes what we can do with this, and there is a lot data that we are going to talk about now.

In fact one of the first things that was done was that Bevacizumab was tried in metastatic breast cancer with a number of different cytotoxic chemotherapies. In particular this is RIBBON-1 which we at the University of Pittsburgh participated in, which is a trial as shown here, where that 1200 women with first line metastatic breast cancer who had not been treated yet were given a choice of chemotherapy, either Capecitabine, taxanes or anthracyclines. They were randomized 2 to 1 to chemo and Bevacizumab or chemo with placebo. They were treated in this sort of progression and about have of the women went on to receive second line chemotherapy and they were given
Bevacizumab, all patients, about half of the patients on the trial chose to get Bevacizumab off study in this particular trial.

In this trial just showing you in terms of the response rates with Capecitabine there clearly was an improvement in response of about 40 to 50% as you can see from this graph, and that was significant with the taxane anthracycline arms, the responses went up from about 38% to about 52%, again an improvement of about 30 to 40%, and again most patients in this trial as you can see here had measurable disease as you can see here.

In terms of regression free survival that was also improved from about 5.7 months with placebo to 8.6 months with Bevacizumab. And again there was an independent review committee which actually looked a little bit better in terms of the progression free survival benefit, about 6 months to almost 10 months, which was statistically significant, this was with the Capecitabine arm of the trial. With the taxane anthracycline arm of the trial again when the independent review committee looked at the data there was a significant improvement from about 8.3 months to about 10.7 months, which again is an improvement of about 23 to 24% in relative terms, which is fairly substantial, and I think as you can see on this graph again even out as far as 24 months there is still a decent amount of long term non-progressors compared to the taxane, to the non-Bevacizumab arms of the study.

This is important because we’ve had a huge debate right now going on in the breast oncology community about what to make of this data given the fact again that people are debating about
whether there is a survival benefit or not. I think I’d like to point out there that there clearly are a
greater percent of non-progressors out at about 2 years with the Bevacizumab arms of this trial than
the non-Bevacizumab. But as I said before, the issue really in RIBBON-2 is the issue we had - in
RIBBON-1 is the issue really that we’ve had now in the ECOG 2100 trial which basically is that the
one year survival rate with the taxane anthracycline arm is basically the same, the one year survival
rate looks a little bit better with the Bevacizumab but as you can see here really there is no significant
improvement in overall survival in RIBBON-1. One of the reasons for that may actually be as again
that half of the women in the trial crossed over to receive Bevacizumab in the placebo arms of the
study, potentially diluting out any survival benefit.

So another trial that’s very kind of in this vein really is a trial called AVADO, which was done in
mostly in Europe, in the United Kingdom, David Miles, an investigator in the United Kingdom was
the principal investigator of this trial. And again looking at AVADO, this took a dose of Taxol, which
is a very commonly used regimen for metastatic breast cancer in Europe and gave it with escalating
doses of Bevacizumab, patients were treated until progressive disease, then at that point they were
actually offered open label Bevacizumab either with continued dose of Taxol or with second line
chemotherapy, and I have to say that about half of the women again receive second line open label
Bevacizumab on this trial potentially diluting out any survival benefit.

And what you can see in this particular trial is again I think when we look at the stratified has a ratio
here, although the absolute benefit is not huge, about 2 months, the stratified reduction in the risk of
progression is about 33%, which is highly statistically significant, something that we would say overall actually does benefit the patient. And again I’d like to just point out here, if you look at the tail of this curve there clearly even out at about 30, 36 months almost doubled the amount of non-long term non-progressors in the Bevacizumab dose of Taxol arms than in the Bev – that the dose of Taxol placebo arm of the trial. And again this runs in contradistinction to the fact that in these trials, in this trial there is really no difference in survival, this 30 and 32 median survival months in the placebo arm and the 15 mg/kg arm of dose of Taxol are essentially the same.

So again we were left a little bit kind of concerned about this and the US FDA was concerned about this and has continued to be concerned about this, given the fact that we do have in a number of trials an increase in response, an increase in the amount of not – of long term non-progressors and an increase in progression free survival, there’s no overall survival benefit. So this brings us to the last of these series of trials, a trial that we actually at the University of Pittsburgh here were the lead investigators on, on the principle investigator of RIBBON-2, which again is a trial now where we take women in the second line as opposed to the first line setting. So these are women who have progressed with first line chemotherapy for metastatic breast cancer and are randomized to receive the following.

So in this particular trial these are women with previously treated metastatic breast cancer that are pre-stratified actually as to whether they are ER PR positive or ER PR negative, what chemotherapy they received and the interval from first metastatic breast cancer diagnosis to first progressive disease,
and as you can see here they are the typical regimens I think we would use as second line therapy, taxanes, Gemcitabine, Capecitabine, Vinorelbine, and again they are randomized to any one of these four agents with or without Bevacizumab treated ‘til progression and there was no allowance for open label Bevacizumab on progression, so this actually we think may be a better way of looking at overall survival from these agents because we are not diluting out the women by having them receive open label Bevacizumab on progression.

And what you can see here, again in, in consistent with the other trials is the progression free survival benefit in the Bevacizumab arms, as you can see here a lot of patients are censored in this trial and these two arms tend to come together so really in terms of non-long term nonprogressors, and again one could argue the reason these arms come together is because we stopped the Bevacizumab on progression, again consistent with the theory that we have which is that you have to continue the Bevacizumab to get continued progression free survival benefit to block progression, to block regrowth of the tumor which has shrunk. You know if you stop the Bevacizumab at a median of 7.1 months you have all this time here where you are not receiving it and therefore these two curves can come together, we are not going to see a long term nonprogressors in this particular trial, so it does make a lot of sense, but there is a, there is a progression free survival benefit. There was no overall survival benefit in this trial when we look at all patients. We’ll talk about this in a few minutes. Again this was with about 54% of the patients having died in this trial.
This trial gets really interesting when we start to look at various subgroups, both some were exploratory but some were actually preplanned. One of those was we looked at what kind of chemotherapy the patients received, and what you can see here, at least in some of this, is that when we look at all patients it’s about again, about a 22% risk reduction, when we look at taxanes and Capecitabine, we really get substantial reductions of about 3 months, or substantial improvements of about 3 months in terms of progression free survival. When we look at Gemcitabine however in this particular study, when we look at the Gemcitabine here what you can see here, because it’s a lot easier to use this as opposed to using the other thing, you could see here there’s only really about a one month progression free survival benefit and actually if anything in this small Vinorelbine arm of the trial really we see almost nothing. So you know in fact if anything a detriment.

So it does appear at least, again, these should be interpreted with caution due to the small sample size of this cohort but on the other hand what I think you can see is that there may be some sort of chemo dependence on what kind of chemotherapy you use with Bevacizumab, at least in metastatic breast cancer. And we do this for individual taxanes. What’s interesting is that again this is nanoparticle associated Paclitaxel, Docetaxel or Paclitaxel, it doesn’t really seem to matter, you seem to get a benefit across all subgroups of patients.

So this is actually kind of interesting but I think what is even more interesting is this, is this analysis based on risk factors. You know when we look at all of the patients, and in particular when we look at patients who are ER, PR and HER2 negative, okay, and in fact most women in this trial were
HER2 negative, it was actually a – it was a requirement, an entry requirement for the trial. What you can see here is that in the women who were ER, PR negative there is a substantial progression free survival benefit here, you can see 2.8 versus 6.5 months, 2.7 versus 6.0 months. So there seems to be most of the benefit actually, there’s a benefit in the ER positive subgroup but really the substantial benefits of a vast, of Bevacizumab in the treatment of metastatic breast cancer do appear to be in this triple negative subgroup of patients, and potentially and again we are investigating this, and we will likely have this data presented at ASCO and so again we may update this talk to discuss this data. We are actually going to present survival data, overall survival data of this triple negative subgroup at this year’s ASCO meeting.

So really these are kind of the messages to ponder. I think in first and second line therapy there is a clear benefit to Bevacizumab and progression free survival, there is a clear benefit to all taxane formulations, a benefit to Capecitabine, a possible benefit with Gemcitabine, but again I think that if we look at all of this is the lack of overall survival benefit you know discontinuation of the Bevacizumab after first or second line progression, which is consistent with some of our models of how we think Bevacizumab works, and I think that you know this is really a matter of some huge debate right now and there is going to be a lot of information at this year’s ASCO meeting that hopefully we will be able to update you on in a couple of months.

The question really then becomes does Bevacizumab add benefit as neoadjuvant therapy, that is therapy before surgery and to this we can look at a trial called GEPAIRQUINTO, which was
presented at this year’s San Antonio meeting by Günther von Minckwitz and his colleagues from the Austrian German study group and it’s really interesting that in Austrian Germany just about every woman who gets neoadjuvant therapy for breast cancer can go on a clinical trial, but this is the decision tree, women who are HER2 negative actually went on to receive Epirubicin Cytoxan with or without Bevacizumab. They were assessed after 4 cycles, if they were responding they went on to receive Docetaxel versus Docetaxel and Bevacizumab.

And if we look at this trial, again this just shows you the design of the trial as I kind of mentioned before, but when we look at the results there does not seem to be any difference in terms of pathologic replete response rate to women receive EC Docetaxel versus EC Docetaxel Bevacizumab. In terms of the breast conservation rate, that is the number of women who were able to have a lumpectomy or some sort of breast conserving surgery as opposed to a mastectomy, it was again about the same. These are one of the measures that we use when we look at kind of whether a therapy is effecting in the neoadjuvant setting.

It’s interesting though when we look at pathologic replete response rates, according to patients subtypes, so we can see very interestingly that there is about a 50% improvement in the rate of pathologic replete response if a patient was ER PR negative. And again this is, this is interesting because it barely does not achieve statistical significance. So this may suggest that again we may have found a subgroup that benefits the most from Bevacizumab at least in the neoadjuvant setting.
There was a trial called NSABP-B40, which is a very similar design to this trial, it’s some ways different, it will be presented at this year’s ASCO meeting and again we’ll update you on this I think after that meeting.

This also has some kind of – some consequences for other trials that are currently ongoing, NSABP-B46 is a trial of node positive, high risk node negative patients who are stratified based on the number of nodes they have, then randomized to Docetaxel, Doxorubicin Cytoxan, Docetaxel Cytoxan Cyclophosphamide or TAC, Docetaxel Cyclophosphamide Bevacizumab, so TAB, I’m sorry. And again the idea is to see number one whether we need an anthracycline and number two, if we do not need an anthracycline, does the Bevacizumab here add anything to overall survival?

The other big trial with Bevacizumab that’s currently ongoing is an intergroup taxane study where women with first line metastatic breast cancer are randomized to receive one of three different taxane like regimens, Paclitaxel and a particle Paclitaxel or Ixabepilone with Bevacizumab. And again these are the two major trials that likely may or may not be practice changing in the next several years.

So let’s change gears a little bit and talk about novel anti-HER2 new agents, are we going to see them kind of in clinical practice in the next couple of years? And the first one has to do with Pertuzumab. Pertuzumab is a humanized monoclonal antibody, a HER2 new dimerization inhibitor, it’s the preferred receptor for HER1, HER3 and HER4. HER signaling is implicated in cancer cell proliferation and survival, Pertuzumab inhibits both HER2 homodimerization and heterodimerization
and we can just show in this particular cartoon what tends to happen is that you can see here on the right hand side Trastuzumab blocks one part of the HER2 receptor, Pertuzumab blocks the other part of the HER2 receptor and basically Pertuzumab blocks the dimerization of HER2 to HER3 and may actually be synergistic with Pertuzumab together. And in fact this has been done. There have been a number of Phase 3, Phase 2 trials of heavily pretreated patients who have failed multiple Trastuzumab containing regimens, and in this particular case you can see here this is a Trastuzumab, Pertuzumab trial alone showing an overall response rate of about 24%, which is quite high in this setting.

So these drugs have also been studied in the neoadjuvant setting, in this particular case in a trial called NeoSphere, where neoadjuvant Pertuzumab or Trastuzumab is used in the following combinations: this is a trial where women with locally advanced or operable, inoperable breast cancer, or operable breast cancer, I take that back, are randomized to receive Docetaxel Trastuzumab, Docetaxel Trastuzumab Pertuzumab, Trastuzumab Pertuzumab or Docetaxel and Pertuzumab, they all then have surgery and then receive anthracycline based chemotherapy to get the standard of care for their disease.

And what you can see here in this particular study is that adding the Pertuzumab to Trastuzumab Docetaxel, or Trastuzumab Docetaxel here what you can see here is that you go from a 30% pathological complete response rate up to a 46% pathological complete response rate and actually just from the two antibodies alone you can see here you get a 16, a 17% pathological complete response rate. When we look at triple negative breast cancer however we see the following, or at
least ER PR negative HER2 positive breast cancer, we see the following: that we go up to a 36% pathological complete response rate from Docetaxel and Trastuzumab and actually it goes up to 63.2% when we use Docetaxel, Trastuzumab and Pertuzumab, and in fact Trastuzumab and Pertuzumab together, two antibodies with absolutely almost really no side effects has a 30% pathological complete response rate, which I think is really dramatic.

In terms of side effects just to kind of be clear on this, really the only side effects we really see are those that are associated with Docetaxel, fever, neutropenia, as you can see here, neutropenic infection, etc. You can see here the Trastuzumab Pertuzumab arm of the trial really has very, very few side effects. There was one episode of congestive heart failure which I’m you know again is something that we always worry about with Trastuzumab in general.

So this has led to a large Phase 3 trial in the metastatic setting called CLEOPATRA. And in CLEOPATRA 800 women with HER2 new positive metastatic breast cancer were randomized to Docetaxel, Trastuzumab and placebo or Docetaxel, Trastuzumab and Pertuzumab, the results of this trial hopefully will be announced within the next year and I think this may lead to Pertuzumab being integrated into the standard of care for metastatic HER2 new positive breast cancer.

The other drug that I think is very important to think about, and there is Trastuzumab DM1 and the idea behind this is to actually link a chemotherapy directly to Trastuzumab, and this chemotherapy is called Maytansine, it was developed almost 40 years ago, was abandoned because it was too toxic,
but this allows us to direct chemotherapy in very small doses to HER2 new positive breast cancer cells in somebody. And you can see here what happens in this cartoon, Trastuzumab DM1 binds to the receptor, it’s internalized into a lysosome, the lysosome dissolves all the protein and then releases the Maytansine inside of the cell.

Other than that in this trial there has been a few Phase 2 trials in this, again in women who were heavily pretreated with anti-HER2 new agents, there is a response rate of about 40% which is quite dramatic. The major grade 3 or 4 side effect being thrombocytopenia to this agent, and again when we look at another trial that was done in patients who were being treated with multiple therapies, anthracyclines, taxanes, Capecitabine, Lapatinib and Trastuzumab what you can see here again with the median number of agents in this trial being 7, the mean duration prior to Trastuzumab being over a year and a half, or Lapatinib being at least 7 months, you can see here that there’s a response rate that’s fairly significant of about 33% in this setting, which I think is quite high. And so we are all very, very excited about that drug and hopefully there is a large trial called AMELIA where that drug is being compared to Lapatinib Capecitabine that will likely be presented in the next year or so.

And then another anti-HER2 new agent is Lapatinib which is a small molecule tyrosine kinase inhibitor that binds to the HER2 receptor on the internal side as opposed to the external side of the receptor, in this particular trial I think a lot of us are familiar with in women who had progressive HER2 new positive metastatic breast cancer were treated with either Capecitabine or Capecitabine and Lapatinib, this trial was stopped early because there was a doubling of the time to progression in
the arms of the trial that had Lapatinib and Capecitabine versus Capecitabine alone, leading to this approval of this drug for the treatment of metastatic breast cancer.

What’s interesting is that we then tried, a lot of us who are medical oncologists interested in breast cancer did a large trial where women randomized who had been heavily pretreated with multiple other agents were randomized to Lapatinib or Lapatinib and Trastuzumab, the idea being the combination therapy would work better than one or the other. And in fact this was done. And this particular trial which has now been published in the Journal of Clinical Oncology what we can see here is that there’s a 28% incidence of progression free survival at 6 months versus 13% with Lapatinib alone, which I think is quite nice but it’s even more important there does appear to be a slightly significant if P is .026, the P value in this trial I think for significance was .05, and you can see here the hazard ratios don’t cross 1, and so what you can see here in this particular trial there is an improvement in progression free survival from 41% with Lapatinib alone at 12 months to 56%. So this is actually a regimen that gives a survival benefit in heavily pretreated metastatic HER2 new positive breast cancer, so we are all very, very excited about the combination therapy.

And in fact what’s even led to more of this excitement is again a neoadjuvant trial that was presented at San Antonio earlier this year, or late last year, last December and what we can see in this particular trial is that women with invasive operable HER2 new positive breast cancer were randomized to receive the Lapatinib and Paclitaxel, Trastuzumab Paclitaxel or the combination of Paclitaxel, they all
then had surgery, they all then had 6 – 3 cycles of FEC followed by a year of an anti-HER2 new agent again to give them roughly the standard of care for their disease.

In terms of safety the biggest side effects were what we would expect from Lapatinib to be honest with you, the biggest ones being diarrhea, a little bit of LFT abnormalities, hepatic abnormalities, and a little bit of neutropenia. You can see here these are more dramatic in the Lapatinib arms of the trial as opposed to the Trastuzumab arms of the trial. But what I think was very striking in this trial is that the combination of Lapatinib and Trastuzumab both in terms of pathologic replete response and replete response both in the breast and the lymph nodes was almost 50%, was 46% in the combo with everything, 51% when you just look at the breast itself, but still almost a doubling of pathologic replete response rate in these anti-HER, in these HER2 new positive neoadjuvantly treated patients. So I think that we are all very, very excited about this data and combination therapy may at some point become the standard of care for this disease, although I think we are still waiting.

But we do have this trial called ALTTO, which is an adjuvant study in which women who with HER2 new positive metastatic or HER2 new positive early stage breast cancer are randomized to receive after all their chemotherapy is over Trastuzumab for a year, Lapatinib for a year, Trastuzumab then Lapatinib or the combination, and I think we all are now expecting this combination arm to be the best.
I think for the final thing that we are going to talk about here and then I’ll stop is where are we with PARP inhibitors in triple negative breast cancer? Again, I said that triple negative breast cancer is a very aggressive form of metastatic breast cancer and so we are all kind of trying to figure out what’s the best treatment for this and again I think that we’ve had a lot of work on this, I think some of the most exciting work was presented at ASCO almost 2 years ago by Joyce O’Shaughnessy and a group from US Oncology for this particular trial, we really investigated how PARPs you know can actually work to inhibit the growth of triple negative breast cancer, and this cartoon just shows you this in brief. Basically if we give someone with triple negative breast cancer a platinum based chemotherapy what you can see here is that the platinum forms DNA adducts. These DNA adducts then induce the expression of PARP that’s polyribosomal phosphorylase, it’s the – it’s one isoform, there are 7 different isoforms of this enzyme. This actually allows base excision repair and allows the DNA to be repaired. However if you have a PARP inhibitor, in this case BSI-201, which is intravenous PARP inhibitor, what tends to happen is that you cannot get this base excision repair, you have these single stranded breaks in the DNA and then when the DNA tries to replicate you get a double stranded DNA break. That’s usually repaired actually, and that’s usually repaired by a complex of proteins of which two of the comp – two of the components of that complex are the BRCA1 and BRCA2 protein products. If you don’t have the elements of this complex you get double stranded DNA repair that can’t be repaired. The cell has also to double stranded DNA breaks, the DNA is rearranged in a broad variety of ways that’s all scrambled and the cell basically dies.
And so the idea here is that if you have cells that are BRCA1 or BRCA2-like, you know with triple negative breast cancer the thought is that some of these cells even though it’s not associated with inherited breast cancer can act like a BRCA1 or a BRCA2 cancer, you can actually get synergy. And so that’s the idea behind using PARP inhibitors with say platinum agents in triple negative breast cancer. And in fact I think what we are finding in these trials is that we may have to actually enrich our patients for BRCA1 and BRCA2 when we do those trials going forward. But this just shows you the trial, this took 121 with metastatic triple negative breast cancer, randomized them to receive Gemcitabine and Carboplatin which is again regimens that are thought to add double stranded or single stranded DNA breaks to the DNA, or DNA adducts to the DNA and then with or without BSI-201. And the patients were restaged after every 2 cycles, and again these results were quite dramatic. They were published in the New England Journal of Medicine about 3 or 4 months ago, and I believe in February, or late January of this year, of 2011. You can see here in this particular trial is that the median progression free survival with Gem-Carb alone is 3.3 month versus about 7 months when we added BSI-201.

When we looked at overall survival, you can see here, which I think is even more dramatic, the overall survival of these patients was about 6 months went up to about 9.2 months at least in this preliminary data. The final data was published in the New England Journal Medicine. So this led to a big phase 3 metastatic triple negative breast cancer study and what you can see is in this particular trial it’s very interesting, this trial randomized and accrued about 600 women with triple negative breast cancer in the United States in about 6 months. That we estimate is about 15% of all women
with metastatic triple negative breast cancer. So the accrual in this trial was very brisk, it just – it just tells you, you know, how desperate we are for a new therapy for triple negative breast cancer. But interestingly enough the trial was completed in January, 2011, and interestingly the week after, actually the same week the New England Journal of Medicine paper came out, BiPar and Sanofi Aventis, the companies that make BSI-201 issued a press release saying the trial did not meet its combined end points of overall survival, progression free survival. So we are all wondering what the trial actually is going to show, and again though we’ve presented at the ASCO meeting in this year, and hopefully we will have an update to the CME presentation to talk a little bit more about that going forward.

So to kind of summarize where we are with these hot questions in metastatic breast cancer is the following. What is the current state of the use of metastatic – of Bevacizumab in metastatic breast cancer systemic therapy? I believe it’s still okay to use it specifically in the second line. I think that’s probably where we are going to end up using this. I think there is still a lot of debate, there’s an FDA analysis of this whole topic that’s going to occur at the end of June of 2011 and hopefully we’ll know the answer. Are novel anti-HER2 new therapies ready for prime time? I think they are very close, I think within the next 12 months or so I think that we will see Pertuzumab potentially as a novel new agent that we’ll be able to use. And then finally, what about novel therapies, PARP inhibitors in the treatment of triple negative breast cancer? I’m not really sure at this point, I think everything has kind of been messed up a little bit by this announcement and hopefully by the ASCO this year and with our
updates at the CME presentation we’ll have a better answer of everything PARP inhibitors are going to be. So again, thank you very much for listening to me and I hope you’ve enjoyed this.