DR. LARRY NORTON: Lisa Carey, UNC, will complete the morning, pre-lunch, by talking about anti-angiogenic therapy.

DR. LISA CAREY: Thank you, everybody. The bad news is that I'm the last talk before lunch; the good news is it's on anti-angiogenic agents in neoadjuvant therapy, so there's a lot less data to review than the people ahead of me.

So, there are a number of agents that are either developed or in development targeting angiogenic pathways. The one -- obviously, the furthest along -- is bevacizumab, although there are a number of others targeting VEGF, moving all the way down to the small molecules that are generally multi-targeted but also coming through.

The rationale for including anti-angiogenic strategies in neoadjuvant therapy is quite obvious to everyone in the room. There was an augmented response in the Stage IV setting, not only in E2100 with paclitaxel, but, in fact, the response rate was augmented even in the earlier phase 3 trial with capecitabine using bevacizumab. Since [in] the neoadjuvant setting, we often have large tumor bulk that we're trying to deal with, an augmented response is a very attractive feature.

These drugs are broadly applicable. The side-effect profile is typically non-overlapping with chemotherapy so there's rationale to believe we should be able to include them to one extent or another with most of our regimens. Similarly, they're non-cross-resistant with the existing multi-modality therapy. So, the rationale for enthusiasm is quite strong. On the "but" column -- on the other side -- we have to consider the fact that these drugs do have issues regarding wound healing, which, of course, is a bigger issue in the neoadjuvant setting than in the adjuvant setting.

We are, again, dealing with large tumors and we're asking the drugs to normalize existing vessels -- which brings up some separate concerns and things to think about as we move forward, and that's that there may be some reason to believe in a biologic discordance

between the primary, large tumor with existing blood vessels, and the micro-metastatic disease in which you really are trying to prevent neo-vascularization.

Similarly -- and in an area that we don't have much data, but I would advocate for people doing research -- is the question of whether or not the balance of pro-angiogenic factors is, in fact, different when the primary tumor is still in place versus when it is removed. That's something that hasn't been studied effectively.

And, finally, the big issue for the neoadjuvant setting, in addition to all the other settings for these drugs, is we have no effective way, at this time, for selecting the appropriate population [in which] to use them.

So, there is a reason to consider anti-angiogenic strategies as synergistic with chemotherapy. Many cancer cells do express VEGFR1 and 2, and so they may be directly impacted by the angiogenesis inhibitor. Similarly, chemotherapy can have effects in the tumor microenvironment and help to normalize the tumor blood vessels and may also have direct effects.

Chemotherapy itself -- although it's not the topic of this talk -- chemotherapy itself can be administered in a way that is more anti-angiogenic, specifically the administration of low-dose, more continuous drugs, which is well known to have effectiveness even in otherwise resistant tumors. If you then take the metronomically administered chemotherapy -- as is shown here in a classic study in a preclinical model –- vinblastine administered metronomically has an effect; DC101; a VEGF-targeted strategy also does. And if you add the two of them together, you see synergy.

So, the clinical data we have -- and I'm going to highlight a couple of studies -- one from Sandy Swain's group looking at bevacizumab with chemotherapy in inflammatory breast cancer. In this study with 21 patients, bevacizumab was given for one cycle as a single agent, then combined with AT given at conventional doses and schedules -- this is non-

metronomic administration. Dropped out all of the bevacizumab and chemotherapy for a four-week wash-out period, then surgery followed by adjuvant bevacizumab.

The clinical characteristics -- again, this is an inflammatory cohort so these are all Stage III and IV, typically high-grade, largely ER and HER2 negative; and about half of the patients had pathologic evidence of inflammatory disease in addition to clinical.

In terms of toxicity, although generally well tolerated, the usual suspects reared their heads in the bevacizumab administration, including hypertension. There were five patients of the 21 with Grade 1 bleeding; two patients had significant declines in [LV]EF. If you take all comers, the EF decline was about six percent -- recognizing this is an anthracycline regimen. Wound complications occurred in nine and included prolonged seromas, incisional separation, and failure to close.

This is important to remember, because in the neoadjuvant setting, again, we're going to have a lot more closeness of the surgical administration with the bevacizumab. If you look at the metastatic colorectal cancer experience, the wound-healing complications are still seen there even though that surgery, of course -- typically it happened considerably beforehand, and is about two percent if you take all of the trials together.

And that's the reason for the black box that I've faithfully reproduced here, suggesting that a 28-day wash-out period be included.

And, vis à vis the earlier conversation, we need to think about this in terms of the sentinel node procedure, also.

From an efficacy standpoint, there was a modest effect, with about a 70 percent partial response, no clinical CRs, and pathologic complete response occurred in one out of the 13 who went on to surgery. This group is a high-risk group, and the estimates right now are that about half of them remain progression-free at two years. The investigators did

look at DCE-MRI and did show some changes with DCE-MRI with the bevacizumab. This did not correlate with response.

Some very interesting biologic correlates were pursued in this study; and I show you here some of the data that they published looking at phospho-VEGFR2, looking at the single-agent component and showing that there was a decrease in this biomarker with single-agent bevacizumab that persisted through the chemotherapy portion of it. They did not see a change in VEGF or VEGFR2.

Using a different antibody in the bottom picture, you see that they still see a decrease in the phosphorylated VEGFR2. Interestingly, the two patients who subsequently were found to have progressive disease did have an increase in this particular biomarker -- again, supporting the idea that we need to find biomarkers that will correlate with our clinical effectiveness of these and other drugs.

It looks like apoptosis was the main finding in terms of biologic impact of the single agent, as shown here. This, again, persisted throughout the chemotherapy portion, but this is what was seen just with the single agent. They did not see a change in proliferative index as measured by Ki67 or in microvessel density.

Another study that is similar, but actually administers the chemotherapy in a metronomic fashion, was CWRU 3100. It was presented at ASCO last year. This is a randomized, phase 2 study of 49 patients, unresectable disease. The patients received weekly dose of Taxol, with or without bevacizumab. Again, a four-week washout, and then surgery followed by an anthracycline. Of the 49 patients, 24 received the bevacizumab and 25 did not. Overall, they had about an 80 percent response rate, and they did not see a difference between the two arms in response.

Toxicity they report as not significantly different, but they did note that five of the patients out of the 24 in the bevacizumab arm did have wound-healing complications, and

three of the 25 in the docetaxel-alone arm. They looked for circulating biomarkers of response and found no difference in a number of them, but they did see, as shown here in the red line, a spike of the plasma VEGF in the bevacizumab-containing arm that was not seen in the chemotherapy-alone arm.

So, I'm going to raise a couple of issues as we talk about this sort of, admittedly, somewhat modest effects clinically using classical parameters that has been seen in these very small studies to date.

The first is, it's not clear that our traditional association of response in the primary tumor with outcome necessarily holds as true with anti-angiogenic strategies as with cytotoxics. If we think about it, the primary disease is a macro-metastatic setting; whereas what we're measuring in terms of disease-free survival is generally the micro-metastatic setting.

Doug Hanahan has made some distinction in his animal models between what he considers to be intervention trials, where you're trying to prevent the development of overt disease, in a sense like our micro-metastic setting, versus a regression trial, where you're trying to reduce the bulk of an existing tumor -- in a sense our macro-met or our primary tumor.

And they've published some interesting data that I show you some of here. In the early setting, which is that 13.5 middle panel, they use some anti… small molecules -- anti-VEGF small molecules – against… in a transgenic mouse model. In that setting, both SU5416, which is a VEGF-targeted agent and SU6668, which is a little more multi-targeted -- both worked quite effectively.

However, when they try to do the same thing in an established tumor model, with regression, they really did not see the same effect and they saw it just with the 6668, not with the 5416. They postulate that there may be other pro-angiogenic factors that were

the reason for this; and, in fact, what they found in that study was that it may be important to target pericytes in the established tumors as well as the endothelium itself.

So, if this is the case, our measurements in the primary tumor may not be in fact as relevant for what we're looking for eventually with disease-free survival.

And I also point out that the number of the small molecules that are currently in development -- they have a widely varying kinase specificities. The ones that were relative in the Hanahan model earlier were the PDGFR and FGFR, regarding pericytes.

So, we do have a couple of trials that are very relevant for this and are the large neoadjuvant studies, in addition to many smaller studies that are ongoing. One of the nice things I'm going to mention upfront is that both of these studies require upfront research tumor biopsies as well as blood specimens; and I think this is going to be an increasingly important component.

CALGB-40603 uses a paclitaxel backbone for chemotherapy, with or without bevacizumab that's given through the first half of AC preceding surgery.

The next one is NSABP-B-40 -- similarly, uses a docetaxel-based backbone, with or without bevacizumab through the second cycle of AC, then surgery.

So, I'll summarize by saying that VEGF-targeting, added to chemotherapy, we know is effective in Stage IV and provides a strong rationale for pursuing it in early breast cancer; and, in fact, there are large neoadjuvant studies that are in the process of either… started or in development.

The issues for us to keep in mind is, that we really haven't an effective way to establish the right patient population -- that's true of all the settings. But we have to keep in mind, in the trial designs, to be very mindful of the wound-healing issues. And, finally, I think

we do have to, as we move along, be very careful that we don't automatically make assumptions about the neoadjuvant model across all interventions, until we have proven that that is the case. And, really, it supports the routine inclusion of biologic endpoints in these studies. Thank you.