DR. LARRY NORTON: So, all the speakers, come on up. Nancy thought I should lead the

discussion here, because I have a cold and my voice is bad, and this is a rare opportunity

to have me say very little. (Laughter)

DR. NANCY DAVIDSON: I only said portions of that, Larry. (Laughs)

DR. LARRY NORTON: You know, the big question for the day, of course, is not is there are a

lot of interesting biology? But, how does the preoperative systemic treatment paradigm

or approach allow us to gain more information? And we had a lot of discussion about

standards and everything this morning -- we won't rehearse that -- and some of you have

already addressed this.

But I thought this would sort of start things off as we're going to get to the questions:

maybe if you could just give one sentence each, or two sentences each, in your own

areas, of how the model of using drugs before surgery is going to enhance the questions

that you want to answer. Ian, you've already done this two seconds ago, but I'll give

your sentence, if you want.

DR. IAN SMITH: Well, I'd just repeat: I think there's two reasons for doing preoperative

hormonal therapy. The first is to downstage to avoid mastectomy or perhaps to make

inoperable operable. And the second is as a predictor, using molecular markers, for

which patients would do very well on this treatment alone and which patients are going to

need chemotherapy added in.

DR. LARRY NORTON: Judy?

DR. JUDY GARBER: I think in the triple-negative setting, or the basal-like setting that…

where we need to find better targets for additional therapies -- this is an ideal system in

which to do research, and there are a sensitive group of tumors for therapy outside of

research trials.

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DR.LARRY NORTON: Lisa.

DR. LISA CAREY: Well, I talked about this a little in the talk -- about the challenges of trying
to take the neoadjuvant or preoperative setting and then assuming that it's the same in the
adjuvant setting. And I think we have some experts -- one standing at a microphone,
handily -- who can speak to that even better than I can. But I do think the preoperative
setting, for all of these things, gives us a great opportunity.

We talked about biologic correlates. In fact, one of the things we didn't talk about as
much, but is a valuable thing, is finding imaging correlates of whatever clinical endpoint
you're interested in; and I think the molecular correlates are going to be key for all of
these. And, blessedly, most of the trials nowadays are being designed with them built in.

DR.LARRY NORTON: Aman.

DR. AMAN BUZDAR: I think the best example is that study which we carried out at M.D.
Anderson. With less than 50 patients, it showed the efficacy and the superiority of
trastuzumab. It took us 7,000 patients, and about maybe two years later, you come to the
same conclusion. I think the preop models are very useful to evaluate the value of novel
agents in that type of setting, and you get the answers very quickly.

DR. LUCA GIANNI: Well, elaborating on that, I think that we will eventually succeed in
deriving predictors of efficacy rather than response in preop systemic therapy setting; and
if this works, it obviously will open a completely new era in conducting clinical trials.

DR. NORMAN WOLMARK: I think I have very little to add to what's already been said -
- I agree.

(Laughter)

DR. LARRY NORTON: Um, you know, I think the big issue that we're all… You know, we're all hoping that response or some biological change in the tumor's going to predict long-term benefit for the patient; and I think, you know, there's a little bit of data that it might -- some data that we've seen that it actually might not, and I think that's… there's this underlying issue.

I mean, a surgeon… I'll just mention the surgeon that I was talking to about it, he says, "You know, if you were trying to develop antibiotics and you said, 'don't cut the abscess out but let me take some cells, some bacteria out and give you antibiotics for a while and then take some more bacteria out', do you think I'd learn anything about the design of antibiotics for treating infectious diseases?" And I think, that's… you know, we've got to consider the possibility that we aren't going to learn, and we will get biological parameters in response to therapy; but long-term benefit, in terms of actually curing people -- we may not see. And I think, you know, maybe we'll get back to some of these issues if we have time later on in the sessions. George?

DR. GEORGE SLEDGE: Sledge, Indiana. Lisa, I have two questions about neoadjuvant anti-angiogenic therapy that I'd like you to enlighten me on. So, first, given the current data, do you have any comfort whatsoever that pCR would be a useful endpoint in the neoadjuvant anti-angiogenic setting?

And, second, with regard to wound-healing -- given that when you've been on a monoclonal antibody for three, four, five months, you have enough antibody hanging around, so that 21 to 28 days is ridiculous to believe that it will no longer have a biologic effect -- that waiting 21 to 28 days will make any difference for wound-healing.

DR. LISA CAREY: I feel like I'm sort of the straight man (Laughs) because I think he'd actually rather answer his own question.

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DR. LARRY NORTON: No, just bounce it back to him. Say, "George, what's the answer?"
(Laughter) Go ahead.

DR. LISA CAREY: You know, I think we're not ready to throw the baby out with the
bathwater here. I think, in reality, while there may be some circumstances where
pathologic complete response is fully predictive of long-term events, this isn't that
circumstance. And, blessedly, all of these trials appropriately include the short-term
endpoints but go on to the appropriate long-term endpoints so that we can see what the
relationships are. And I agree with you: I think there's great concern that we are taking
lessons from one therapeutic type and applying it to a completely different mechanism --
and that may not be feasible.

I do think that we can gain a lot of information and there's probably some relationship,
but it's certainly not one that is… we're not going to be able to compare apples to
oranges here.

Regarding the second question about wound-healing, you know, I share your concern.
You know, in reality, these are drugs with several-week-long half-lives, and whether or
not this becomes a bigger issue in these neoadjuvant settings is something that's going to
have to be monitored very carefully in these trials that have a few weeks -- basically,
about one half-life where the drug is not being given.

MALE SPEAKER: Steven (unint.), Charlotte. A comment and a question on what Dr. Buzdar
just said. If small trials do show us a great benefit in pathologic complete response, I
think it's important that we acknowledge that the confidence intervals are very broad, and
that may or may not be borne out by much larger trials. But the question related to that
is, if those predictions are true, then how do we explain B-27? Because there was no
survival advantage, despite of a two-fold increase in pathCR.

DR. AMAN BUZDAR: I think B-27 is a different study which I would like Norman to talk

about it. But the thing is, that model… I totally agree: the sample size is small. But the

study was stopped because we were hoping for a 41 percent pathCR rate, and it was over

60 percent; and even the lower limit of 95 percent confidence interval was above that.

So, I think the thing is, that's why we were very confident that these observations were

real. It has stood the test of time for the past three years.

DR. LARRY NORTON: Norm, do you want to add something to the mystery?

DR. NORMAN WOLMARK: Yeah, well, number one, you know, I'm perturbed by the

nihilism that seems to be expressed for pCR as a robust indicator of outcome. It most

certainly is a robust indicator of outcome. The fact that we didn't see a survival

advantage by adding the four cycles of taxane in B-27 I don't think in any way refutes the

value of pCR.

I think, in retrospect, that B-27 was under-powered, that we calculate based on the data

from B-18 and B-27, that even a 30-percent pCR would've probably resulted in no more

than 2.2 percent incremental benefit in overall survival; and Soon Paik will review those

models tomorrow.

So, you know, I think that I am certainly not prepared to abandon the elegance of using

the preoperative model and pCR as an indicator of the efficacy of a regimen; and I think

we've really just started. I mean, we have a whole host of biologics that are coming

down the pipeline. I think that the Herceptin data are intriguing -- the Herceptin /

trastuzumab data are intriguing -- in the preoperative setting, and I think that the

bevacizumab trial is something that I'm really enthusiastic about.

Will it have problems on wound healing? Well, we'll find out very quickly; and we'll

find out using the randomized prospective clinical trial.

DR. LARRY NORTON: Ian?

DR. IAN SMITH: It's not so much that pCR isn't a good indicator of outcome, which, I
     think, it's very convincing. The question is, does a difference in pCR between two
     therapies -- is that enough to indicate that there's going to be a long-term difference in
     outcome? Because that's the premise behind the design of all sorts of trials; but the B-27
     doesn't seem to support that.

DR. LISA CAREY: Moreover, if there isn't an alteration of pathologic complete response,
     does that mean that you will not see a benefit? And I think that's… I mean, I share your
     enthusiasm for pathCR, and I think for cytotoxics, it's very clearly established as a very
     good predictor. I'm just concerned that, in some of these trials, if there isn't an
     augmented pathCR rate, that people will begin to lose enthusiasm for the combinations;
     and I think that would be an incorrect assumption.

DR. NORMAN WOLMARK: I completely agree. I think, you know, that it's incumbent
     on us to develop a predictive profile for the non-pCR's as well, because we've seen that
     they're a highly heterogeneous group.

DR. LARRY NORTON: I'm just going to add a sentence of bias in this: you know, what
     kills us in cancer is metastasis -- you know, cell growth is what we're attacking with most
     of our agents. And so it's entirely possible that we can have anti-mitotic agents get
     shrinkage of things and not affect metastasis or even accelerate metastasis -- you know,
     conceivably, as it sometimes happens in animal systems. And, so, whether there's a
     correlation between pCR rate and long-term outcome, they reflect on the kinds of drugs
     we're using, all right? And with some agents we may see the correlation, with other
     agents we may not.

And I think as we get more complicated regimens -- with bevacizumab, etc. -- that we may see results that may be hard to explain, but are fairly easy because of the fact that cancer is a process that's not just cell division -- it's also metastasis and invasion. Matt?

DR. MATTHEW ELLIS: So, first a point of clarification -- Judy, that UCN01 irinotecan study is in the metastatic setting -- it's not a neoadjuvant study. But I'd love to do it in the neoadjuvant setting, but that's not the place where we're starting.

And then with Ian, a point of agreement: so, I agree that the clinical responses are a poor surrogate, particularly with respect to that HER2 issue as well as long-term outcomes. But if we look at proliferation data, it's very clear that the ER-positive, HER2-positive tumors have a high Ki67 which is not affected well by letrozole; and that's perfectly consistent with the long-term outcome of the adjuvant trials.

And then, third, a question for you, Ian: I noticed that your *JNCI* paper you focused very much on that two-week biopsy. However, many of these tumors show a dip in Ki67 which then rebounds at four months.

And I suspect -- and this is from data I'll show you tomorrow -- I suspect that the four-month Ki67 is even more predictive of long-term outcome, because it includes those patients who rebound. So the question is: have you looked at the long-term outcome in your studies, looking at the four-month Ki67 as opposed to the two-week?

DR. IAN SMITH: You make a very good point; but the reason we haven't looked at the four-month -- the reason is this: that the attraction of the two-week, is that you get a very early measure of whether the treatment's going to be of benefit or not. The four-month value is the same as pCR; it may be very valuable; but, by that time, a large chunk of your treatment's over. So, the attractive thing about the two-week is the fact that you get your predictive measure so quickly.

DR. MATTHEW ELLIS: Yeah, but you may be fooling yourself, Ian…

DR. IAN SMITH: Exactly. For some… I agree with you--

DR. MATTHEW ELLIS: …because of the rebound phenomenon which is very common with
    that Ki67 data; and four months is still better than five years. And it may actually tell
    you a lot about whether you should give chemo or not or other systemic therapy; because
    you've captured not only intrinsic resistance, but rebound resistance.

DR. LARRY NORTON: I want you two folks to talk about this offline and come back to us
    with the right answer. (Laughter) Because we've got very smart people there that have to
    ask questions.

DR. IAN SMITH: In one sentence, though: you can only use the four months in your classic
    neoadjuvant program; but you can use two weeks in anybody.

DR. LARRY NORTON: Martine?

DR. MARTINE PICCART: Martine Piccart. Yes -- this is a question to Professor Wolmark.
    So, the NSABP's starting new neoadjuvant trials with very aggressive, complex
    chemotherapy regimens with or without bevacizumab. And I am wondering: don't you
    think it's time to stop contaminating these trials of chemotherapy with the luminal A
    patients, who are probably not helped by chemotherapy that much? And, if you include
    them, it's background noise and it complicates the interpretation of the trials?

DR. NORMAN WOLMARK: It may or may not. You know, I think, certainly, the
    point's well taken. I think we need to try and enhance the population for, you know,
    maximum benefit. I really don't know about luminal A's and bevacizumab or HER2
    positive -- unlikely that you're going to have luminal A's that are HER2-positive in the

other subsets -- but, at this point, I am not convinced to the degree that I would eliminate those subsets from our bevacizumab trial.

DR. LARRY NORTON: Okay. Bill. We're running into a lot of time pressure, so…

DR. WILLIAM WOOD: Quick question for Luca Gianni. To me, much of the excitement of the model is not just that it will let us identify the pathCRs, but it will let us identify the group of patients who are the non-responders. Are you interested in addressing therapy targeted to that non-responsive group, than trying to affect the whole population by working on the ones we can't currently help?

DR. LUCA GIANNI: I think this is a very important question, because it addresses the possibility of applying selection criteria to the neoadjuvant setting, which I think is what you should do. If you ask me when we worked out the study with Genomic Health -- what we did was on purpose not deriving a predictor of pCR. We think that, or I think is, that it's more clinically relevant at this stage to establish a predictor of resistance to whatever type of treatment. Because that is immediately applicable, while predicting pathologic complete response cannot be used to negate the same therapy to other patients who will not achieve a pCR.

DR. LARRY NORTON: Okay, Mitch, Joe, and then I think we have to stop.

DR. MITCH DOWSETT: I'll try to make it quick. On the way over here yesterday, Ian and were just saying that it would be great that if, in B-18, in the pre-menopausal group, we actually had data on menstruation -- i.e., whether the patients had actually become amenorrheaic on treatment or not, because there might be some underlying data which would sort of support the POETIC trial that Ian described. Then you showed, Norman, today, the data on the less than 50's, which makes that an even more seductive and interesting possibility. You might have that data, but I suspect you don't.

DR. NORMAN WOLMARK: I suspect we don't either.

(Laughter)

DR. MITCH DOWSETT: (Laughs) Can I -- just to follow it up? Have you looked at it in terms
of continuum of age, rather than just cut off at 50?

DR. NORMAN WOLMARK: Not as yet.

DR. LARRY NORTON: Joe, you're on -- last question.

DR. JOSEPH SPARANO: Well, it was sort of a related question, given the provocative results
of the updated analysis from B-18, and the fact we've all had now about -- what -- two
hours to think about it. Is it now a legitimate research question again to ask the pre-
versus post-operative question?

DR. NORMAN WOLMARK: Well, you know, I would like to have some confirming evidence
for what the B-18 observation was. I think the most likely explanation for that
observation is that it occurred by chance, just as we hypothesized in 2001. On the other
hand, the fact that the data are still there, you know, that's the way the data are. I would
really like to have some additional information from an unbiased, unrelated source to
either confirm or refute that information before we decide that it's a real phenomenon or
not a real phenomenon. It may or may not be. I mean, if I had to guess, I would go either
way at this point.

DR. LARRY NORTON: It's actually a novel thought, when you do unplanned analyses, you
know, rather than generate prospective studies, which we obviously can't afford to do in
every case -- to have other people look at their datasets. Then it's not really data-
driven… It's data-driven by your data; it's not data-driven by their data. And it might be

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a way of confirming fishing expeditions, in other words. It might be a way of actually learning something.

DR. NORMAN WOLMARK: Yeah, it would be nice if somebody else would fish.

DR. LARRY NORTON: Ian, last comment, and then we have to go on.

DR. IAN SMITH: It just relates to that, and the point Mitch was making. The effect you showed was a late effect -- it started after five years. That's an endocrine effect. That's what happens with ovarian suppression. So, it's worth looking at more.

DR. LARRY NORTON: Okay, we thank you all. Thank all the panelists, thank the audience. And we're going to go on to… I think it's Edith Perez and George Sledge.