DR. CLIFFORD HUDIS: So, we’re going to re-convene, as promised. We’re going to start with the Q&A from the last session, and then, at about two o’clock, we’ll proceed to the panel itself. In terms of the questions from last time, obviously, if you have any, please make your way to the microphones, either upstairs or downstairs, and we’ll call on you; but while we’re waiting…

These talks obviously generated any number of complex and interrelated questions. And, along the morning… through the morning, I had one which I think we have to struggle with a little bit. And that is this -- historically, in-breast response for any chemotherapy regimen has been numerically higher than any other site of response. This is a bigger issue than it may seem at first, because the issue here is that we’re using the in-breast response, to greater or lesser degree, as a surrogate for the ultimate outcome, and the ultimate outcome is actually being driven by the viability and responsiveness of the micrometastases. And I put this open to the panel: how are we going to cross that particular, wide gulf? You can defer to Don Berry if you want, since he’s not here. (Laughs) But, you know, Soon -- you’re the right one, because that may be a big part of what goes on in B-27.

DR. SOON PAIK: Possibly. That’s why I regard pCR, as Don [Berry] suggested, as one of the correlates that we can use but not as an absolute surrogate. I think it’s very important to realize that. He made a great point.

DR. CLIFFORD HUDIS: So, I want to follow it, and then we’ll go to the questions. It raises the possibility that part of what’s going on here relates to tissue-specific gene activation and stromal factors, which we’re sort of pointedly ignoring through all of this. And I wonder, Matt -- or anybody looking at -- Lajos -- you know, as you drill down on these tissues, how are we going to account for tissue-specific variability that may have a lot to do with what’s going on in this regard?
DR. MITCH DOWSETT: Can I just make two comments on that? One thing, clearly, in the IMPACT study anyway, the gross data on the biomarker Ki67 did reflect outcome in ATAC. And what was great was having the combination arm in that which performed really very similarly and against many people’s expectations. So that was a good control. So, at least at a gross level, the micrometastases in that circumstance seem to reflect what was going on in the primary tumor.

There was a statement made, though, by Stephan (ph.) Brown last week. It was an almost off-the-cuff remark in the St. Gallen meeting. And certainly Nancy picked it up. Where he said something to the effect of, the genetic makeup of the micrometastases’ cells in blood was different from the primary’s; which I think was a bit of a surprise to many of us, when we think about the macrometastases being relatively similar. And it may be just that in both cases, they’re different; and in one case he’s looking for differences, and in one case he’s looking for similarities. But I think it’s an important issue as to what quite… what those differences might be.

DR. LAJOS PUSZTAI: I think the question that you brought up, Cliff, about the in-breast responses and the clinical response rates, which are very high, is actually very important. And it really has a very unsettling connotation.

So, most people respond, but the vast majority do not benefit from these more intensive therapies. So, clearly, the curves show that there is actually a difference -- it’s an eight percent difference in recurrence-free survival. It’s a very interesting coincidence, that this eight percent absolute improvement, which is borderline statistical significance, based on Dr. Wolmark’s presentation -- it’s the exact same number which is the absolute numerical improvement in pCR rate. So, 10 percent of the people -- actually, 10 percent more -- achieve pCR. And there is a 10 percent improvement in recurrence-free survival.
So, one way to put this together is, really, the only people who benefit are the ones -- the majority who benefit, really, is this very small sub-population who is pushed from a residual disease category to this pathologic CR category. And this is an entirely possible explanation for the results.

And it clearly shows that responses are very far from being any valuable surrogate for long-term outcome, because long-term outcome is very little, whereas, almost everybody has responses.

DR. SOON PAIK: I think one of the strongest arguments against your notion is that, you know, if there is a... extreme difference between primary tumor and the micrometastic site for the gene expression pattern, then we shouldn’t have been able to, I think, develop Oncotype assay or 70-gene assays, because that’s all based on primary tumor and it still is able to, you know, predict the outcome and response.

FEMALE SPEAKER: I think part of my question was answered by your question, Dr. Hudis. But I still -- you know, when I came to this conference, I wanted three questions answered, at least partly answered. One was, who are the patients whom we target in neoadjuvant therapy? Number two is, what is this role, this glorified role, of pathological complete response? And number three is, how do we recognize these non-responders more than the responders?

Because, you know, if our goal is tailored therapy, which is... seems to be the biggest goal that they’re doing this neoadjuvant therapy, is, how do we, then, stop giving something that, you know, this patient’s not responding...?
Now, I’m willing to forget the first two questions because I realize there’s a lot of controversy there, and there’s really not one school of thought.

But I just want to ask you, regarding this tailored therapy -- it would be really nice if there was some kind of guidelines that can be universally used. At least, you know, we talked about radiological evidence of early response. But, you know -- think about this: this is not something that can be applied to a community hospital, you know, for several years down the road. First of all, we have to prove its reproducibility and then it depends on the person who’s doing it. And there’s a lot of questions there.

So, the one thing that can be done is clinical response. That’s something that every oncologist can see. You know, you give two cycles of AC, no change in the tumor. Is that the patient we stop giving AC and switch to Taxol? I mean, that is a question that… Has that been looked at? And do you have any guidelines regarding that, which I think then can be carried on to a community oncologist, at least in the interim period before we know more answers?

DR. KATHY PRITCHARD: I don’t think we know the answer yet. I think that… I’m not even a panel member, but I’m going to put my oar in, and I’m going to say that I think when a patient doesn’t respond after two cycles with disease in the breast, it can’t be a good thing. But I think we don’t actually totally know how that plays out in the long haul in terms of whether they would do better with a switch. Some of the limited data we have -- for example, the Aberdeen study -- shows that everybody does better with a switch, whether they’re responding or they’re not responding. I don’t know if other people would like to comment on that, specifically.

DR. LAJOS PUSZTAI: So, you know, the only difference is that you actually know this. I mean, if you would do this same chemotherapy in the adjuvant setting, you would not
know it. I mean, how does this benefit you? Or how does this benefit the patient? Or how does this benefit the progress of science?

So, really, what neoadjuvant chemotherapy brings into the light is that, yeah, very often these treatments actually… I mean, you don’t understand who benefits from it and who are the individuals who don’t. And the only way to actually find these markers is to use the treatment as neoadjuvant therapy. So, I think it’s important.

The separate issue is that, why is this really relevant for research? And what’s the value of this in clinical practice? And, again, I think many things are known about neoadjuvant chemotherapy. And one thing which is known is that, if you give the same chemotherapy before or after surgery, the outcome is the exact same. And it’s a fact -- it’s been shown by four randomized studies.

Now, you can make more refined question -- is there a subset who might possibly be harmed… and, sure, there might be a subset, but you don’t know who they are. And the same goes for any kind of chemotherapy, adjuvant chemotherapy -- is there a subset who you might hurt by giving Taxol, AC, rather than CMF. There might be, but you don’t know that.

DR. CLIFFORD HUDIS: Matthew, push your red button.

DR. MATTHEW ELLIS: So, I think when we’re thinking about medical oncology, there are two real extremes. The extreme is when you know precisely the target you should target, and you have a drug that works against that target. So, the example there would be GIST tumors of the stomach or…. CML, for example. And the other extreme is when you haven’t got a clue what the genomic structure of the tumor is, and you’re using relatively non-specific drugs, and you don’t really exactly understand how they work. And that is
essentially where you are when you’re discussing Taxol or cyclophosphamide in untargeted populations of patients with… you know, unselected populations of patients with breast cancer. So, my only sort of thought for the day is that, the one thing that these preoperative studies will do, will provide material on which we can build genome maps, and allow those maps to actually be clinically annotated.

Because one of the problems that we’re facing right now – you know, you open the pages of *Science* and *Nature*, and there’s these -- I won’t say, “irritating”, because they’re incredible tours de forces -- but, basically, the paper says something like, “The breast cancer genome is incredibly complex, and look! Aren’t we clever -- we found 250 mutations in 10 samples.” And that actually is not very helpful. What you need to put is all those 250 mutations in the context of events that had happened to patients. So, to try and begin to get at this, at Wash U, together with all my… many of my colleagues in the room -- we’re trying to take the engine of the genome-sequencing centers, and the genomic analysis techniques we can do now, and to do all that wonderful, high-throughput genomic analysis in the context of these studies. And NHGRI are very interested in this, and I think… So, we’re beginning to get… we’re beginning to get to a system where we’ll get answers; but right now, we don’t have any.

DR. CLIFFORD HUDIS: So, we’re all sensitive to, really, I think the crux of your question, which is, “What do we do in practice versus what are we talking about from a research point of view?” And I think the answers are decidedly different. And, in practice, most of this is not ready for implementation, and that’s the bottom line. At least, I’ll speak editorial, and not for everybody else. Brian?

DR. BRIAN LEYLAND-JONES: Leyland-Jones, Emory. I just wanted, Mario [Marco], to ask you one specific thing, and Lajos, to ask something a bit broader. So, Mario [Marco], you showed the data on the hormone-negative, HER2-positive… sorry -- yes, hormone-
negative, HER2-positive data on one of your slides which showed really, quite a lot worse 5-year DFS and 5-year OS, as opposed to the triple-negatives, and I just wondered if you had any explanation for that? I trust this was pre-trastuzumab, but the difference was quite striking, just how much worse the HER2-positive group did than the triple-negatives.

DR. MARCO COLLEONI: This is one of the explanations -- this is pre-era… the era pre-trastuzumab. The other explanation I have is that, in our institution, we frequently used cisplatinum-containing regimen in the preoperative setting -- the old ECF(?)… So, we suppose we treat quite adequately the patients with triple-negative subtypes. Whereas, we didn’t treat it adequately in the patients with HER2-positive disease.

DR. BRIAN LEYLAND-JONES: Interesting. So, Lajos -- the broader question: in as much as I love your trial design -- the new neoadjuvant one. Basically, most of your neoadjuvants, at least in our practice, who are HER2-positive, will get trastuzumab prior to surgery. Your non-responding ones, basically, you wouldn’t expect to do well on sort of the phase 1 part, and I’m just wondering what kind of patients you could enter with equipoise onto that trial? You know, in the splay between the full gamut of ER-positive -- whatever -- in order to show a difference. You know, in other words, what kind of patients you would randomized. And I’m really asking this in the light of Martine’s comment yesterday about excluding luminal A’s or the ER-positives for that kind of study. So, I’m just wondering what quite answer you’ll get out of that, because I would have thought that a lot of your ER-positive ones would generally have got into other trials anyway.

DR. MARCO COLLEONI: Personally, I agree with Martine in the sense that I would not candidate the patient with a luminal A to a trial with chemotherapy questions -- I mean, dose-dense versus anthracyclines and taxanes. I believe these patients should be candidated to endocrine questions. And what I saw in this conference, there are several
trials on endocrine treatment in endocrine-responsive patients, but mainly focusing on post-menopausal patients, mainly, possibly, frail post-menopausal patients. I didn’t see anything about pre-menopausal patients, which represent about 60 percent of the patients candidate to preoperative therapies, in our experience. Two-thirds of these patients are ER-positive, or endocrine-responsive disease. And I believe we need questions -- targeted questions -- for this very large population, as we have in the adjuvant setting, where we have trial like the TEXT trial, the SOFT trial with specific questions for that specific population. This was the message I would like to explain with my presentation.

So, several populations should be treated with a really targeted treatment.

DR. LAJOS PUSZTAI: Brian, the study that I showed is not a randomized study. It’s really a molecular triaging study. So, if you are HER2-positive, then you get trastuzumab plus standard chemotherapy. In our case, it’s weekly Taxol, and then, subsequently, FAC.

And if you are predicted to have complete response to neoadjuvant chemotherapy, regardless of the ER status -- then they get neoadjuvant chemotherapy. And there the study ends, with surgery. So, possibly, you can add additional treatments, including hormonal therapy for the ER-positives, if you want to, particularly if their ER-sensitivity signature also predicts sensitivity.

The third group is the group who does not do well and we predicted that they would have residual disease to Taxol-FAC; but, at the same time, are highly sensitive to endocrine treatment based on another predictor. And those individuals will get neoadjuvant endocrine therapy for six months, and then surgery. And we try to learn what early surrogates might be there -- like cell-cycle arrest, or what kind of pCR rate we see in that highly selected endocrine-sensitive group. And, post-operatively, of course, they will continue with five years of tamoxifen. And they surely have an option to get chemotherapy if they want to, (unint.) they understand that we predict that they won’t do
well with it, or they probably won’t be helped, or the majority of that group won’t be helped, by it.

And the fourth group is the group that does not do well, according to our predictions, with any of these treatments. And they just get triaged into an investigational treatment.

And then we look at the entire group, at one point, and see what pCR rates are (unint.) And if we see a pCR rate, a combined pCR rate, of 25 percent… greater than 25 percent… (DR. LEYLAND-JONES: Yes, it was that box on that left-hand side that confused me.) DR. PUSZTAI: …we will think that this is a better approach at least to increase pCR rates, than just giving the best chemotherapy to everybody. And, of course, time will tell whether these people actually will live longer, or have less recurrence. But we will certainly track that, too.

DR. KATHY PRITCHARD: The left microphone.

MALE SPEAKER: I wanted to follow up on Jo Anne’s comment about translating pathologic complete response into clinical practice. And my particular question is, what is the metric, from a regulatory, from a reimbursement, from a guideline or standard of practice point of view, by which you could look at data, four or five years from now from the various preoperative studies that we have, and say, based on these changes in pathCR in these subgroups of patients, therefore we should offer x treatments to y patients? Because it seems a challenge to me -- and notwithstanding Don’s enthusiasm for modeling -- that we still don’t have the metric. We don’t know if a 15 percent improvement in pathCR leads to a two percent or one percent improvement [improval] in overall survival. So I guess the question is, what sort of things, from a regulatory point of view, would one like to see before adopting this as a standard of care for patients?
DR. JO ANNE ZUJEWSKI: Well, I think that’s why I had it as a question. You know, right now, from a regulatory point of view, since pathCR, at least as far as I’m concerned, hasn’t been… and the FDA as well… you know, it’s not a true surrogate for the outcome that we care about. And I really don’t know how to get there from here. You know, I suspect that we can, if we concentrate on the subtypes for whom pathCR is useful, like those who get them as opposed to those who don’t; and then we would really have to prospectively validate it -- I don’t see another way around it. And I’m concerned, as I mentioned, with the triple-negative, that, because of feasibility, we won’t get there. You know, I’m hopeful that we’ll increase the pathCR, and I’m hopeful that we’ll be able to do a randomized trial. And maybe if we have a more or less… a homogeneous group in that particular subset, it could be prospectively validated; but those are a lot of “if’s”. You know, and I do think it’s a problem.

DR. FRANKIE HOLMES: Frankie Holmes, Houston. Terrific session today, and I just want to put on the table, since today we are more biologically directed than yesterday -- the question that was raised in the context of addressing response: is there a role here for a simple blood test, like circulating tumor cells, in those patients who have them -- would that be useful? I was looking around for Dan [Hayes] but I think he isn’t here. Just to put on the table, recognizing that many patients don’t have them; but would that be useful, especially in that patient who didn’t respond after two cycles of AC?

DR. SOON PAIK: I think that’s a very interesting question, and we’ve been trying to incorporate that kind of question into our trial. But, I think the problem is that -- for example, circulating tumor cells, you need so much blood to be able to detect one tumor cell in adjuvant setting, that we thought that it’s actually practically not doable in this kind of trial population. You actually need about 30 mL of blood to get one cell. And, you know, if you look at standard deviation and all that, I don’t know how you can really
make out of the data that’s generated with only a few cells and their changes during the course of treatment. I think that’s the major issue.

DR. JOANNE ZUJEWSKI: I just wanted to clarify that. You know, in the metastatic setting, there’s a lot of circulating tumor cells, so they’re able to pick it up -- you know, 7 tumor cells or 5, or whatever it is; but in the adjuvant setting, it’s not as easy -- there’s not as many cells floating around. So, the real challenge is, as Soon mentioned, with having to draw a lot of blood, not picking up many cells, and then wondering if those are truly cancer cells or just a cell floating around, is still an obstacle to using that type of test in an early-stage disease setting.

DR. KATHY PRITCHARD: In view of the time, we’re going to take two more questions, so, the left microphone and then the…

FEMALE SPEAKER: Pat (unint.), NCI. It’s a question for Soon Paik. If I heard you right, you used a 90-gene prognostic signature in your talk to separate good from poor. Is that a previously known one? A new one? Can you provide some information?

DR. SOON PAIK: No -- this is purely based on this population, and just cross-validated within the population. So, it is extremely preliminary data that needs to be confirmed in other studies. But, until we get the…

FEMALE SPEAKER: And how did you get it? How did you classify the data to get that signature? And does it look like any of the other known signatures?

DR. SOON PAIK: There is a specific procedure called Supervised Principal Components analysis, developed by Stanford group, that actually allows you to look at the data… pull out the genes that correlate with clinical outcome and then do a Principals Component
analysis to put them into the two groups. But I just presented the data in two, equal-sized groups; but you can divide them in any way you want; it’s actually a continuous variable.

FEMALE SPEAKER: And does that signature look like any of the other published signatures?

DR. SOON PAIK: Yes, actually -- it very much looks like OncotypeDX assay; it’s mainly driven by ER, HER2, and other genes that are very familiar to us. So, it’s actually… I’m showing that as an example of the research question that you can answer with the tissue. And, obviously, regardless of what kind of signature you use or combination of some classical markers, you will probably divide them into exactly the same thing.

FEMALE SPEAKER: And just a quick comment to Cliff re: your previous discussion on these signatures versus site-specific growth. You’re all right. I mean, from my read of the literature, there are metastasis or poor-outcome signatures, clearly, in primary tumors. But, layered onto that, there are site-specific growth signatures, as well as differences in circulating tumor cells.

DR. CLIFFORD HUDIS: Well, actually -- just to add a little more granularity -- I was really referring to the stroma, which is another layer on top of that. So, I agree with you.

FEMALE SPEAKER: The stroma in the breast and stroma in the lung are two different things.

DR. CLIFFORD HUDIS: Right. Final question. Thank you.

MALE SPEAKER: Dr. Dowsett, you showed data that patients who had high Ki67 levels at their excision did markedly worse than those who didn’t; and you interpreted that as saying that if you have a high Ki67 at baseline and don’t get a pathCR, you’re going to do poorly. And I wondered -- but those patients really have two strikes against them: one
is that they have... they don’t have a pathCR, and the other is that their tumor doesn’t respond in terms of reducing proliferative index after therapy. And so I wondered if you could tease that apart by specifically looking at the patients who had high Ki67 at baseline, and then, at the excision, had residual disease but did have a reduction in that Ki67? So, in other words, if you have... if you have a baseline Ki67 and don’t have a pathCR, are you destined to do poorly? Or if your tumor is responding to Ki67 reduction, then that can salvage things?

DR. MITCH DOWSETT: Very briefly, I don’t think we’ve done it as cleanly as you’d like; but the implications of the data as a package do support that -- that those patients that have those very high Ki67 levels at excision do very poorly, and clearly those are the patients that didn’t get a pathCR. Yet, we know that the patients that generally have high proliferation have a greater tendency to get pathCR. So, I think we essentially need to do what you’re asking, to give you a cleaner answer.

MALE SPEAKER: Right. So, basically the patients who had high Ki67 at baseline, if that goes down without a pathCR, do then those people do well, or are they still destined to have high recurrence rates? I guess is the question.

DR. MITCH DOWSETT: The patients who go down but don’t have a pathCR?

MALE SPEAKER: Right.

DR. MITCH DOWSETT: I mean, they have an improved likelihood of response. We’ve showed... Andreas’ data showed that quite some time ago, but that was using 21-day data rather than the three-month data.

MALE SPEAKER: Thanks.
DR. CLIFFORD HUDIS: So… Go ahead, Kathy.

DR. KATHY PRITCHARD: We’d just like to thank all the speakers very much, and for all the questions. Thank you very much.