(NOTE: “Primary” therapy here refers to preoperative therapy.)

DR. LARRY NORTON: Luca, hop up here. Let’s continue and talk about the European experience.

DR. LUCA GIANNI: It would be hard to speak after Norman and most difficult to match his way of presentation. So I was asked to give the European perspective and I amended the title, “Some Potentially Relevant Points of the European Experience”. I do not represent all of the European experience, but I will try to give you an opinion that is mostly personal, with a European twist.

Okay, so basically this is the start and I would like to start with what has already been said and that is -- I think that they missed one slide -- and this is the first series of randomized trials in Europe except for Fisher.

And you see that with this type of median follow-up, there were several… Again… Okay, sorry. This is the one. The effect was that there was a really important effect on the breast-conserving surgery that could be applied to patients with application of primary chemotherapy.

And we can skip this [slide].

And the other point that has been already elaborated several times during his talk by Norman Wolmark is that in these slides here there is a clear effect of pathologic complete response on efficacy outcomes as measured by relapse-free and total survival. This is a slide that represented the experience -- at the Istituto Nazionale Tumori in Milan -- but there are several other examples and that there is no need to go ahead on this.

So, basically, the first generation of randomized trials offered the concept that that primary chemotherapy is at least as effective as classical adjuvant chemotherapy -- we

know now that this may be partly amended -- and down-stages tumors and allows for a high rate of conservative loco-regional treatment; but, most importantly, pathological complete response independently predicts for efficacy outcome.

And based on that, there are several questions that were the focus of attention in the new generation of neoadjuvant chemotherapy studies. I know that many of these questions will be addressed during these meetings.

And some of the speakers will again go back to this concept. And this is, how we can improve the rate of pCR? And the other point is, will it improve pCR? Can it improve efficacy? And can pCR be predicted? And if pCR prediction is useful.

And there are several tests that were proposed: how can pCR rate be improved with new drugs -- and this has been tested -- or with new regimens. And that the other point is: whether pCR does improve efficacy. And there was a comparison in between first- and second-generation regimens, and other points.

So let's first talk about the first two questions. And here is, again, a European perspective of the application of new drugs, regimens, and pathologic complete response.

And as you can see, basically there were several indications that either prolongation of treatment, or addition of the taxanes or other new drug, resulted in an average increase of the rate of pathologic complete response that was around 20-plus percent.

I really have problems with this stuff [referring to advancing the presentation slides].

Now the other point that was addressed is the role of new modalities of administration -- here we have Larry Norton and he was the reason and the cause of a flurry of studies on dose-dense schedules and pCR. I will not elaborate on the studies by Gunter von

Minckwitz because he's here and he will talk this afternoon, and I'm sure that he will address part of this presentation.

And what is interesting is that, overall, dose-dense regimens appear to have a similar rate, with few exception, in terms of pCR as the regimens without dose-dense -- except for studies where there was a direct comparison of the dose-dense versus not the dose-dense such as the studies of Gunter and in the study with Untch.

The other approach was that of using sequential regimens; and here there are two studies that are crucial to me, and the one is by Smith -- who's not today to speak about chemotherapy, so I am safe and I can present (laughs). And the other one is, again, from Gunter [von Minckwitz], so Gunter will have to present his own data.

But this study here -- the Aberdeen study -- is something that they think is extremely interesting; and I wanted to elaborate a little bit on this. This is a study that was published in *JCO* 2002 and, basically, patients were to receive four cycles of an anthracycline-containing regimen and then reassessed. And patients with clinical response were again randomized to continue on the same therapy or to receive docetaxel for four cycles, while patients with stable disease or progressive disease were a minority -- one-third of them were switched immediately docetaxel.

And, interestingly enough, if you are resistant to the anthracycline-containing regimen, you don't get really great benefit from the switch to docetaxel; while if you go to continue with the same regimen you get a nice response, but inferior to the one that you can derive from switching to a different and non-cross-resistant regimen.

So, sequential administration of the non-cross-resistant regimens was clearly superior in this study; and not only was superior in terms of response, but this also resulted in a superior efficacy outcome at three years.

So let me now talk of a study [the ECTO study] that I know pretty well because I had the privilege of contributing with Gianni Bonadonna in designing the study back in 1995. And, in this study, that was conducted in Europe in several countries, what we basically did was to select patients with tumors larger than 2 cm and randomize them to:

--> Receive surgery followed by a sequential regimen of doxorubicin followed by CMF.

--> Or, as in Arm B, to receive surgery followed by doxorubicin and Taxol, followed by CMF.

--> Or in Arm C -- the same chemotherapy containing Taxol, followed by CMF, followed by surgery.

And the endpoints were disease-free and overall survival. And the study has enrolled more than 1,400 patients overall.

So, one interesting point is that you can observe already, in the clinical setting, that the administration of CMF causes an advantage on top of the results that you can clinically measure after administration of doxorubicin and paclitaxel.

As you can see, you can move many patients who were originally partial responders to complete response by administration of CMF; and patients who had minor or no response to doxorubicin and paclitaxel -- they can become responsive with clinical CR or clinical partial response. And, overall, the study had an 81 percent of partial responses and complete responses that could be measured after the completed administration of doxorubicin, paclitaxel, and CMF.

And, as already presented by several other speakers, you have an advantage that you can measure in terms of the axillary nodal status involvement in the different arms. And, in red, you can see that 61 percent of the patients who underwent primary systemic therapy

were free of axillary involvement, versus 38 percent of the patients who did not, who received adjuvant treatment after surgery. And there was a shift towards the left of the red bars, indicating, overall, an advantage not only in moving of the few nodes to no nodes, as one might expect.

As in the studies presented before, also in these studies we had high rate of pathologic complete response, including patients who had a residual DCIS, with 23 percent of the responding patients achieving an eradication of the in-breast tumor.

I will not present you the data about the nodal status in these patients, just to say that there was enormous, complete concordance in between patients with tumor eradication in the breast and absence of involvement in the axilla -- that we are 90 percent of the overall patients who achieved an in-breast clearance. So basically it's difficult for me to show results that are different from a subset of patients with in-breast pCR versus those who are in-breast and axillary pCR.

But one of the advantages of going after the analysis is that one of the main planned analyses became mature and we presented this study at ASCO 2005; and one of the comparisons was whether AT followed CMF before surgery was any better than adjuvant. And the data show that, for patients who achieve a pathologic eradication, clearly there is an advantage in terms of freedom from progression, while there is no difference in terms of benefit in between adjuvant and primary chemotherapy. So the only subset who has a measurable advantage is the subset of women who derive an eradication of the tumor by application of primary chemotherapy.

So let's leave that there for a while and consider some additional points. And the other points are whether… can pCR be predicted? And there are classical variables to be taken into account and variables coming from newer tools. And we had stratified our patients according to a series of variables and others were under control and here we have the

analysis -- univariate analysis -- of the association between AT-->CMF and likelihood of eradication of in-breast tumor.

And, as you can see, age, tumor size, clinical nodal involvement, and tumor grade had no association with the likelihood of the eradication of the tumor, while both the estrogen and progesterone receptor status had.

And, at the end of the day, if you run the most important and univariate analyses (unint.), ER status, which also resulted as the only variable independently associated with the likelihood of achieving a pathologic complete response in a multivariate analysis.

So, this is not new -- there are several indications by several papers published in the literature -- clearly indicated, as in this table, that among the 30 or so percent of women with hormone-receptor-negative tumors, there is a prevalence of pathologic complete response that are more frequent than in women with hormone-receptor-positive tumors.

So this is a fact, and here there is just a small sample of the data; but if you go and make an analysis of our study in a multivariate analysis of freedom from progression, which is in these studies, at this stage, the strongest variable associated with benefit -- long-term benefit -- basically, you have that in multivariate analysis, there is an association with response, as expected, with the axillary nodal status, as expected; but, with the hormone receptor status, the association is exactly in the opposite direction as for response.

You remember we have more pathologic complete response in ER-negative, but the long-term benefit is better in ER-positive.

So, is there a reliable factor predicting for likelihood of response to primary chemotherapy? Obviously, ER(-poor) tumors are associated with increased pCR; high tumor/nuclear grade is also associated, in many studies, with increased pCR; and high proliferation index is also associated in increased clinical response.

However, pCR and efficacy are two different things; and I think that key difference and implications are very relevant.

pCR is strongly directly associated with likelihood of improved disease-free survival. But likelihood of pCR, which is higher in the ER-negative, and likelihood of disease-free survival, which is higher in the ER-positive, are differently associated with hormone receptor status in multivariate analysis, so that enriching for ER-minus cases and sorting out ER-plus -- positive -- based on probability of pCR will negate a valid therapeutic options to many patients.

Are there ways to improve the pCR rate in HR-positive [hormone-receptor-positive] tumors? There are a few studies addressing this question and one of these studies is the ECTO II. The design is for ER-positive. We have three different -- slightly different -- backbones of chemotherapy in association with exemestane. Exemestane is acting through a mechanism which is profoundly different from that of tamoxifen; and you may expect, as indicated in pre-clinical studies that derive advantage from the combination of aromatase inhibitor and chemotherapy.

So now: is pCR prediction useful? Okay, I would like to dedicate the last few slides to an analysis of… that we have been performing in collaboration with Genomic Health about the application of the Recurrence Score assay and pCR. Everybody knows in this room what the Recurrence Score is -- basically is a continuous assessment of risk deduced from a retrospective analysis of NSABP trials which correlates with distant recurrence at 10 years; and you have a low-risk group and an intermediate-risk group and a high-risk group. And, usually, the lower-risk Recurrence Score is associated with a low expression of proliferation genes and high expression of ER-associated genes and the reverse occurs in the high-risk group.

So when we decided to make an analysis of what the role of Recurrence Score and the primary chemotherapy, we did that in a study conducted in 90 or so patients at the National Cancer Institute, where patients with locally advanced breast cancer receiving the same therapy -- and sequentially receiving that. And we basically analyzed the expression by RT-PCR in the core biopsies of these patients.

And we have published the indication that, basically, the higher Recurrence Score, as in TAILORx, is associated with a higher likelihood of pCR. So, the cluster of pathologic complete response is all in the high-risk group. Again, for these patients, we have the analysis that pCR do better than no-PCR patients in terms of freedom from progression; and these are locally advanced breast cancer.

But, very interestingly, Recurrence Score… A recurrence from distant metastasis in this subgroup indicates that -- first of all, you have a good value of your Recurrence Scores -- also in locally advanced breast cancer -- to tell you that there are women who really do well. But, please note that here the blue curve, which is for the high-risk, high-Recurrence-Score -- this high Recurrence Score is also the group where you have the cluster of pCR's.

So in the same group you have the best responders as well as the worst outcome; and I think that this is a very relevant point.

So is prediction of pCR useful? pCR is more frequent in patients classified as high-risk according to classical variables -- no expression of hormone receptors -- as well as newer gene-expression classifiers.

Any classifier of pCR should be tested for its ability to predict efficacy with high sensitivity and high specificity in an adjuvant setting, rather than simply anti-tumor activity in the neoadjuvant one. And with this, I would complete and conclude my presentation. Thank you.