Future Directions Panel Discussion

Dr. Aman Buzdar: This is the truly interactive portion of the meeting where there is no set format, and we will talk about future directions in endocrine therapy. What large trials should be attempted? Looking at all of the data, what would you like to see if you had carte blanche?

Dr. Matthew Ellis: My interest, obviously, is the neoadjuvant therapy: it’s extremely data rich and you can learn a lot about the biology of breast cancer in that setting. The question, particularly for my North American colleagues, is what type of trial would increase your comfort with that clinical approach?

Dr. Paul Goss: How necessary is it to do a neoadjuvant trial to answer the very interesting science questions you’re looking at, as compared to preoperative? In other words, does it have to be a 4-month study with a clinical end point to get the data you think are critical? Can we use these early biomarker effects as an end point in a 3-week preoperative study?

Dr. Ellis: The advantage of the neoadjuvant setting is actually using the endocrine agents for treatment. Of course, there’s also been a long-standing debate on how well a surrogate marker predicts a clinical end point. You can argue that clinical response is only another surrogate marker, because the only end points that really matter are relapse and death.

Dr. Buzdar: If we give neoadjuvant therapy the chance to work, the degree of downstaging correlates excellently with the long-term outcome of the patient. If a patient with a T3, N1 is downstaged to T1, N0, that patient is going to behave like a T1, N0.

Dr. Anthony Howell: There’s never been a proper neoadjuvant endocrine trial. By that I mean a study comparing neoadjuvant treatment of, say, 6 months’ duration versus the same treatment given after local therapy in both arms. We need to do those studies.

Dr. Kent Osborne: We certainly accept treating patients with chemotherapy neoadjuvantly and a number of those don’t respond. It’s hard to imagine that a 4-month window is going to make a difference on metastases. If it does, it’s going to be in the smaller tumors. If you limited eligibility to 6-cm tumors or some arbitrary cutoff, watching for 3 or 4 months while you do your neoadjuvant approach is not going to make one iota of difference in the ultimate outcome. It might even help. We don’t know. That’s the study.

Dr. Buzdar: If I could summarize, I think we all agree that a neoadjuvant setting may be a short cut to doing adjuvant trials that require thousands of patients and years of follow-up, whereas the end points could be very easily defined in months if we do appropriate neoadjuvant studies. You are not harming the patient if the patient is being closely followed, and most of these patients are seen on a monthly basis. If a patient is showing evidence of progression, you could always discontinue the experimental therapy and go to chemotherapy or local therapy.

Dr. Ellis: Preoperative biological therapy is probably something we’re going to do an awful lot of in the next 10 or 15 years while we’re sorting out all these different subcategories of breast cancer—recognizing breast cancer as not one disease but all these different cancers and optimizing our strategies for all these.

Dr. Buzdar: Does anybody now want to lead the discussion as to what drugs should be studied and how we should get into this area?

Dr. Ellis: I think a fairly obvious study would be aromatase inhibitor versus aromatase inhibitor plus a P.O. active tyrosine kinase inhibitor targeting EGFR and HER2. I would treat the patients neoadjuvantly for 3 or 4 months, and I’d get as many biopsies as the patients were willing to give me. We’re bracketing the adjuvant setting, because you can get answers in the metastatic and neoadjuvant settings, and then you’ve got this adjuvant setting where it is taking decades to get answers. I think this is going to be more of a problem as we move forward with the biologicals. Take Herceptin: I’ve had patients randomized for control who walk out of the trial. We’re always bypassing the adjuvant setting, and the adjuvant trials we do set up will rapidly become obsolete if we’re not careful. Because the questions we can ask now require 5 years to answer, and in 5 years there are five new drugs and a further appreciation of the different subsets in breast cancer.

Dr. Goss: Another approach would be that all adjuvant trials should have a neoadjuvant component to them. You answer the question and then you verify the answer with long-term treatment. I would be loathe to apply a neoadjuvant result to a massive adjuvant trial because that result cannot necessarily be extrapolated to an adjuvant setting. You’re not going to abandon your standard of care for neoadjuvant results. So you need two sets of trials.

Dr. Ellis: If these neoadjuvant experiments do predict the results of the adjuvant trials that are now ongoing, if that connection is made, then I think you can set new combinations in the neoadjuvant setting as the place where you develop your next adjuvant strategy. Because otherwise, we could overlook many good therapeutic approaches by this, and drugs might get lost.

Dr. Carlos Arteaga: These combinations we’re proposing are novel and attractive, but they have never been done before. So how would you deal with the need for safety data for the combination?

Dr. Ellis: I think you would proceed by metastatic, neoadjuvant, then adjuvant as the drug development paradigm. That would give the safety and activity data first, then the treatment-naive results.

Dr. Stephen Johnston: I think we need to do these studies in the metastatic setting, because we’ve all got plenty of metastatic patients in our clinics, and we’re at the stage now where the interesting endocrine trials are all coming to an end. We do a Phase II trial now and go straight into randomized Phase II design to actually get the safety and efficacy data.

Dr. Steven Come: I come back to the idea of the models again. Are these models getting enough respect when it comes to design of major trials? Is there a disconnect that the scientists are doing the science, and the groups are picking one aromatase
inhibitor? It seems to me that the logical sequence would be to test these things in the models to find what looks best and take the winners in model systems and go to the neoadjuvant and preoperative setting to get biological correlates and go from there into the bigger trials.

**Dr. Osborne:** I think that the models have been useful where they can provide a testable hypothesis. Our model is what convinced AstraZeneca to do the Phase II study with Dr. Howell.

**Dr. Buzdar:** One question which I wanted to pose was the sample size of these studies. If you are looking at modest differences, then even these 3000- or 5000-patient studies may not be adequate unless you wait for another 5–10 years to have enough events.

**Dr. Goss:** That speaks to what clinicians think is a clinically meaningful difference in outcome. We can continue to set the trials at a certain size by saying that's the kind of clinical difference we want to see, and if we don't see it, it's not worth pursuing further. If you're asking, do we have to do bigger and bigger trials to try and pick up smaller and smaller differences, then that's true, we would have to. But I don't think we'll do that.

**Dr. Kathleen Pritehard:** On the other hand, the differences may proportionately be quite large as you get into lower risk groups, although they may be in absolute numbers not that different. As soon as you start to look at any kind of subset analysis, you don't have enough power to do it.

**Dr. Buzdar:** In prevention, is it too early to move any of these drugs into that subcohort of high-risk women?

**Dr. Victor Vogel:** We essentially have to do prevention studies that validate what we already know. But now the doors are getting closed because now we can no longer do a placebo-controlled prevention trial, so we get into this problem with equivalence trials. Do we have to wait for validation in the adjuvant setting for these agents that look very attractive in a prevention model, given that we have no agreed upon intermediate markers that we can use to validate any of these strategies in the prevention setting? In many ways we have a bigger problem, and I wish we had a neoadjuvant model that we could then translate to the prevention setting. We haven't been able to come up with a design other than large prospective randomized designs. But we can't do too many more 22,000-patient studies.

**Dr. Pritchard:** In the preventive setting you've got the additional problem of having to look at other health-related outcomes, which are competing risks in that setting. I would submit that if somebody studied hormone replacement therapy 40 years ago in a randomized design instead of all these observational studies, we would have known a lot more today, and it probably wouldn't have cost us more money but less.

**Dr. Goss:** In regard to surrogate markers of breast cancer risk, the data are growing that estrogen level is a marker of breast cancer risk in postmenopausal women. We're moving toward a point where we may be able to say there's an estrogen dial that can tell the breast cancer risk. If that actually is ever verified, we have with the AIs a tool that can dial the clock the other way.

**Dr. Vogel:** I don't think it's quite that simple. In the prevention setting you still have Dr. Pritchard's problem. What do you do about the bones? What do you do about the pelvic floor? What do you do about cognitive function, if there is any relationship?

**Dr. Ellis:** We have drugs that work as preventive agents, but we don't have a good way of assessing who needs them. This idea that every 60-year-old needs tamoxifen is patently ridiculous. So we need to do much more research on risk factors for sporadic breast cancer. You may need smaller doses of aromatase inhibitor. You may just need to get them down from the upper tenth down to below the lower tenth percentile, and you may need 0.1 mg of letrozole to do that.

**Dr. Vogel:** You make a good point about dose response, but there again, how do we do those dose-finding studies to find the optimal dose in the preventive setting? I'm not sure we've defined the model for those studies because there may well be different doses that would achieve a preventive effect without having some of the detrimental effects.
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