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Progress and Promise, Part IV Panel Discussion

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Question: *Is anyone going to sort out which of the hormonal agents for treatment of prostate cancer (PRCA) is better than the others, or are we going to have to use three or four of them in combination, including combining an androgen receptor (AR) agonist and antagonist?*

Dr. Taplin: One of the important questions to be answered is that if a patient is on one drug (e.g., abiraterone acetate) and their disease is progressing, do you stop the first drug and go to a sequential agent, or do you continue using the first drug and "layer on" other agents. Large, highly powered trials are now under way that are designed to answer this question.

Question: *In a patient who has failed chemical castration, we have a choice of several drugs to use in this situation. Do we know which agent works the best as an initial choice in this situation?*

Dr. Taplin: We do not at this time, and there are no trials under way surrounding this. This is of concern as we are at risk of being in the position seen with kidney cancer, where there are four or five drugs that may be used initially, but clinicians do not know which one to use first or how to combine them.

Dr. Smith: Early experience has shown that there does appear to be a substantial amount of cross-resistance. For example, the response rate for enzalutamide following abiraterone is relatively low, substantially lower than that for enzalutamide up front, and the converse also appears to be true. This is early data, but it appears to be a fairly consistent observation. If this is correct, it would appear that there would not be a lot of additional gain, although that does not mean an individual patient would not benefit. If you accept that the scale of trials needed to determine optimal sequences versus combinations would be massive, it is unsure if the community appetite to do such a trial to inform clinical management would be there. There will be trials looking at combinations, but they may not answer all the relevant clinical questions.

Dr. Lee: [Our group] studied AR signaling in circulating tumor cells (CTCs), and we had the idea that we may be able to identify those men who will or will not respond to a drug like abiraterone. We wondered if any pharmaceutical company would put themselves up to sponsor such a trial, potentially cutting back on the number of patients who would actually receive the drug. We received support to do an abiraterone study to look at AR signaling prior to treatment and see it we can identify these AR signals that are predictors of response to the drug (or lack thereof). They are not all looking to make certain that everyone gets the drug, but this was a challenge.

Question: *Some of the markers we have available for other tumors have very similar character to what I've heard at this meeting for prostate-specific antigen (PSA). Historically, when one has had a biomarker, that was the option available, even when better things come along or it is discovered that the original test is not that good, there are many reasons to stop using it. Although it is clear now that PSA is not ideal, is it causing problems using PSA? Would we be better off if PSA was not being used as a stratification basis?*

Dr. Smith: (Use of) PSA is very challenging, and it is ingrained in the culture, including patient understanding of the disease. PSA as a screening test has major well-described limitations. As a monitoring test, it may be better, but it does lead to substantial confounding in the field. We need intermediate endpoints; we cannot do every trial based on overall survival (OS). In PRCA, we have this distinct problem, as prevalent use of PSA testing leads to biases within other testing, imaging frequency, physician assessment of attribution of events, whether it is due to disease or otherwise. PSA is potentially huge confounder. In the SPARTAN trial, we are using PSA as a marker of high-risk progression, but we are proscribing the measurement of PSA during the trial because it shouldn't be informing clinical management. That would be the onset of detectable meta-

static disease that would mean the need for the next intervention. It would be challenging to change due to the long-standing tradition between patient and physician to measure PSA frequently.

Question (to Dr. Garraway): *On the topic of diagnostics, since we agree that we need other methods of assessing PRCA, other means of biopsy, liquid biopsy such as circulating tumor cells (CTC), ways of predicting responses. You have identified a phenomenon new to most of us, regarding the existence of these chains in possibly the majority of prostate cancer. Is it possible that these chains may have diagnostic utility in some way?*

Dr. Garraway: The short answer is that we would first have to do a study that allows us to detect the prevalence of these chains across a large cohort and see if the presence or prevalence of this event correlates with aggressive disease, which it might. In theory, this is the kind of thing that, if true, could have diagnostic utility, except that right now, there is no way to find it except by sequencing the genome, which is not a valid proposition in any clinical scenario right now. If there was a way we could figure out a surrogate marker for this event, maybe some DNA repair marker we could use as a surrogate, there might be something to discuss. But for right now, it is not something we can move to the clinic in a realistic scenario.

Question (to Dr. Lee): *In the CTCs, you are looking at single gene rearrangements. Is there any possibility of scaling that up to fuse what you and Dr. Garraway are talking about in some way to improve the diagnostics and get us to the point where we have really powerful surrogates from CTCs?*

Dr. Lee: I think that what we've seen with single cell picking from CTCs in patients with castration-resistant disease is that the gene expression profile is very heterogeneous, so I am not certain any one selected cell will accurately portray everything that is happening within that patient. But that is what we hope may be the promise, that we can identify the representative clone. If there is a dominant clone, then perhaps there is a way to marry these two technologies together.

Question: *Is there an opportunity here also to ask a sort of practice of oncology question? As the surplus of riches that we are now the beneficiaries of that you are developing for PRCA are abounding, will the practicing oncologists (and urologists as well) have to change their practice as they use these investigational agents that are now being newly approved and also monitor their patients more acutely and carefully to pick up resistance so that they can go to a second or third-line treatment more effectively? The question is, if these patients are not monitored carefully, might we not foreclose some options or actual recovery for some patients?*

Dr. Lee: With the advent of all these newer hormonal agents, it has been easier for patients to remain in the care of the urologist or the treating radiation oncologist. And medical oncologists are getting patients who are a bit further along in their treatment course. That is when they get referred to us for chemotherapy and the like. I do think that those patients who have recurrent castration-resistant disease should be referred to a medical oncologist as standard practice in that medical oncologists should be managing the care of those patients.

Follow-up question: The concern that has sometimes been expressed to me is that if patients, for example, just go on abiraterone right away as first-line therapy and stay on this orally administered drug for a long time, by the time they may actually relapse significantly they may have foreclosed options of some secondary therapies down the line (e.g., cabazitaxel).

Dr. Smith: This is a fair concern. I think the bigger concern is that, to the uninitiated, there will actually be premature discontinuation of therapy. In studies that demonstrated benefit of abiraterone and enzalutamide, treatment was continued beyond PSA progression, and in some of the trials, beyond radiographic progression until symptomatic progression. A bigger-picture concern in the community is that there will be some premature discontinuation (e.g., in patients with excellent response, discontinuation for a modest PSA elevation), which could be a bad decision for the patient. Another issue is these drugs are comparatively safe and well-tolerated compared to chemotherapy but still require some monitoring, and the necessary tools and interest may not be within the bandwidth of those monitoring (i.e., blood pressure, serum potassium) and other issues related to these medications.

Question: *I worry about the notion that we have an "embarrassments of riches." I don't think we do. Once we have curative therapy, that might be the case, but when these drugs are given in advanced disease, we are still looking at timelines that are measured in months to a year or two for each patient. And we are also seeing cross-resistance between some of these most exciting agents, so what would really be ideal is if we would find a way to incorporate these agents, and hopefully new ones in the future, into curative models. That probably means treating earlier disease, and one of the challenges of that will be how we do those trials in a way that is time efficient. For better or for worse, survival is typically measured in many years. If one does a phase III trial in early disease, one has to be willing to wait 10 years until survival benefit is seen. If we want to look at curative therapies in early disease, what are the valid, legitimate endpoints that can be used in a trial? Is it pathological complete response, is it CTCs, what is it that we would advise regulatory agencies (in terms of what we can measure) to help move these things forward faster?*

Dr. Taplin: There is a big initiative that is being done by Chris Sweeney in our group with Phillip Kantoff and the Prostate Cancer Foundation (PCF) and partners in industry to do a very large meta-analysis of all the adjuvant therapy trials that have been done in conjunction with surgery and radiation therapy to gather that data and look at endpoints in those trials and present it to the United States Food and Drug Administration (FDA). We are trying to get buy-in from them to look at target endpoints, pathologic endpoints, as well as freedom from PSA failure, freedom from metastasis development. I think the answer is out, there is a lot of belief on the part of PRCA physicians that this is long overdue. I think there is some momentum and money behind this effort with a lot of partners to try and to try to move this and the field forward.

Follow-up comment to Dr. Smith: *In the ARN-509 trial, you had to consider what types of endpoints would be acceptable.*

Dr. Smith: That will become one of the early tests. The FDA is willing to work with investigators and sponsors to use intermediate endpoints, deliberately using the term intermediate here instead of surrogate because it's not a surrogate until surrogacy is established. For example, the primary endpoint of the ARN-509 trial will be metastasis-free survival. These will all be review issues. There's no established surrogate outcome in PRCA to date. There are some promising leads; Dr. Taplin mentioned some of those in some important efforts to look at in the future. We can make recommendations; key opinion leaders and experts in the field can have opinions about it, but that is very different than regulatory acceptance. All of these will be review issues, and the challenge for sponsors is that these are $100 million bets on trials and the FDA position is that this has to be a review issue. This is a very difficult place to be.

Question: *How do you explain PSA progression when at the same time patients are responding in terms of bone lesions getting smaller and even soft tissue lesions getting smaller? Are you potentially defeating the effort to define intermediate endpoints in the one cabozantanib trial?*

Dr. Smith: In the cabozantanib trial, we have embedded a novel endpoint, bone scan response, using an FDA-cleared methodology with the hope that with a positive trial in terms of OS, you'd be able to look at the relationship between an intermediate endpoint and survival and potentially use that for guidance in future trials. In the case of cabozantanib, it is relatively straightforward. Some of the known targets of cabozantanib do impact AR signaling and PSA expression through feedback. There is other data from other model systems, other tyrosine kinase inhibitors, that the same is true. I am not concerned about the partial discordance between PSA and antitumor activity, for the following reasons. First, there is not complete discordance, so patients do have PSA declines, and all of those basically respond. The CTC data, which is an independent antitumor effect, also shows responses. To answer this question, we'll have to wait for the full results of the phase III trial.

Follow-up question: *We understand that there are multiple populations of tumors, and some of them have differential control over androgen response. Are there mutations in the androgen receptor that would explain this or other factors?*

Dr. Smith: I wish we had a more thorough preclinical understanding of cabozantanib. There are a couple recent publications that look at this issue. In the preclinical models of cabozantanib, there is very clear impact on tumor, bone, and tumor-bone interactions.

Dr. Garraway: This is going to be true in PRCA resistance, and this has been true in resistance in a variety of targeted agents. I believe we are vastly undersampling the extent of heterogeneity of resistance mechanisms. An example is what tends to happen in melanoma resistance in RAP inhibitors, where you sequence an exome or panel of genes and you recognize the mechanism and think that mechanism is "it." But, in fact, if you look deeper, you can find multiples of those mechanisms, even in the same tumor focus, in different metastases from the same patient. This is likely to be true in PRCA as well, and we also know that there are genetic and nongenetic mechanisms by which resistance arises. I think resistance heterogeneity is a huge issue. It is not surprising at all that you can see a patient responding yet still see his PSA rising, because all that is needed is 1 or 2 foci that are not responding as well and you will see PSA going up. I think we are going to have to come up with a framework of grappling with that heterogeneity at some point.

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