Keynote Luncheon: Emerging Trends, Issues, and Treatment in Late-Stage Disease

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Mr. Simons

Our keynote speaker, one of my colleagues and good friends, Dr. Oliver Sartor from Tulane University, has done a great job in trying to implement research in a very difficult venue. He is one of the leading cancer researchers in the world and has recently brought to fruition our most recently approved advanced stage prostate cancer drug through the strength of his efforts alone.

Oliver Sartor, MD

Thank you, Virgil, for having me. As you probably know, prostate cancer mortality in the African-American population is extraordinarily high, roughly twice that in other populations in the U.S.

Quoting a 1966 Nobel Prize-winning urologist from University of Chicago, Charles Huggins, he believed that there were many failures of endocrine therapy to control prostate cancer, and that is what we now call hormone refractory or castrate refractory or castrate resistant disease, which means that the cancer is progressing despite having a low serum testosterone. This is challenging but it has really become a face of change. There is so much changing right now that it actually changed this morning, which is pretty remarkable; a big phase 3 trial is going to be positive. This is pretty amazing: this is an evolution in understanding, in our current standards, with multiple new paradigms on the rise.

The testosterone receptor, the androgen receptor, is really about hormonally signaling because we have gained new insights into hormonally signaling even in these patients with advanced and supposedly castrate resistant disease. This is the androgen receptor; this is what testosterone will bind to. If you measure the testosterone receptor in patients who are castrate refractory, castrate resistant, it turns out that the androgen receptor is up-regulated, which implies that these cells are trying to get access to the testosterone when it becomes low in the bloodstream. This was an important experiment: Jim Moehler [phonetic], a urologist who was at University of North Carolina and now at Roswell Park in Buffalo, was measuring the tissue levels of various hormones in people in whom he did TURPs. Some of these patients were castrate resistant with low serum testosterone as a consequence of medical intervention. He observed that testosterone is pretty much the same in patients who had benign prostate and normal testosterone in the serum, and castrated patients, and this was predominant in cancer. This did not make sense: why would you have the same testosterone in the tissue derived from people who have a normal testosterone in the bloodstream or a low testosterone in the bloodstream?

A group from the BI Deaconess put together a series of specimens from patients with advanced prostate cancer, which were well preserved specimens to look at analytically. What the researchers found is that the enzymes that were regulating the conversion of precursors to testosterone were significantly up-regulated in these patients who had this castrate resistant or castrate refractory disease. It appeared, when these data were put together with Dr. Moehler's data, that the hormones were actually being synthesized in the prostate cancer tissue itself. We always think about testosterone coming from the testes, and maybe from the adrenal gland, but now we have to think about it from a new source because the cancer cells themselves are synthesizing testosterone, which can be a growth signal.

Now we get into something a little bit more complicated. This is the gene of the androgen receptor right here; there was a discovery by multiple laboratories, from Hopkins, from Mayo Clinic, and what they discovered was that the machinery that puts this gene together to turn into a protein does not always function normally in cancer cells; you end up with what we call alternative splicing. Alternative splicing truncates the androgen receptor: only a part of the receptor is synthesized.

Unfortunately, when you synthesize only part of the receptor, you delete this part of the gene expression, which is the part that binds to the hormones. The weird thing is that this part, which is the DNA binding domain, exons two and three, can still work. Now you have an antigen receptor that does not even require testosterone. In autopsy specimens from patients with hormone refractory disease, these spliced variants are the norm; here are TURP specimens from people who had castrate resistant disease. Now we have to scratch our head a bit because it looks like the cells can not only make their own hormones, they can now make receptors that do not even require the hormones in order to work.

Even though my conclusions on this part of the talk is that the androgen receptor signaling remains a key factor in prostate cancer growth, the prostate cancer switches from what we call a traditional endocrine paradigm, this means that the testosterone is coming from the testes or adrenal gland, to an autocrine/paracrine paradigm, which means the cells are making their own hormone. But some of the apparent mechanisms of androgen receptor activation are actually independent of the ligand. This is getting really tricky: the next real step forward is to be able to take these antigen receptors that are spliced in an alternative fashion and get rid of them. To my knowledge, we just submitted last week the first paper to show that that is possible.

Thinking more pragmatically, not about what is in the lab but what is in the clinic, there are a variety of therapeutic options for castrate resistant disease today. The ones highlighted in yellow are FDA approved, but this is only part of the armamentarium. We have all these secondary hormone manipulations; nobody has ever shown they prolong survival but they all work for a bit. If you end up failing initial hormones, you can still respond to hormones; that is what we do today is we manipulate these things. For painful lesions, you give external beam radiation. For multiple painful lesions, you can use intravenous bone-seeking isotypes. The bisphosphonates do not change any of the natural history of the disease but may decrease fracture rates, which can be important for those with a heavy disease burden; and chemotherapy can be used. We have submitted

our work to Lancet and hope it will be published on fast track. Immunotherapy is creating interest and controversy.

Has anyone here ever been on a clinical trial? Two people have been. That is probably about right; most people do not go on clinical trials. I will show you some clinical trials and I encourage people to think creatively about clinical trials as an opportunity for improvement not only in their personal health but in the health of the field as well because every FDA approval comes through good clinical trials, and they can be conducted ethically. That is the key thing: the ethical conduct. You have to hope the new treatment is going to work, but it cannot be proven to work. There is an equipoise where we sit and try to figure out what really is the right thing to do, and that is where clinical trials are very valid.

For many years, docetaxel, or Taxotere, was the only agent showing a survival benefit. Some large randomized clinical trials were done comparing docetaxel to standard of care, which was mitoxantrone at the time; a modest survival advantage was seen. One tricky thing about interpreting global datasets is trying to figure out where you might be on that curve; it is often hard to determine whether you personally will to benefit. Here, the median time to progression for these patients is about six months. I had two African-American patients in my clinic this week who have benefitted for over a year; I believe if I had not treated them, they would have been dead. There is a lot of variation: the physician must be honest in what can be of benefit, and the patient must be honest in deciding whether to try it. This trial from 2004 showed modest benefit with Taxotere. This is old news; we are moving forward.

Some agents in clinical trials indicate there is a lot of opportunity for progress because the only way that we will have progress is have these clinical trials report out positive. We have new vaccine trials. This anti-CTLA4 was the rage at this year's ASCO because it prolongs survival in metastatic melanoma, which, by the way, has disparities weighted heavily towards Caucasians and away from African-Americans. Angiogenesis inhibitors are being tested: Avastin did not work but we have others on the way. The new antitubular agent is being trialed, as are newer androgen receptor signaling targeted agents. Bone-targeted isotopes such as radium-223 are being trialed, as are compounds called endothelin antagonists. Stem cell related agents, such as stem cell signaling agents, are being trialed. Chemotherapeutic resistance in apoptotic regulators is being studied.

Here are the big phase 3's: this is where the action really happens because this is where the FDA approvals can follow; this is where you can move from investigation to the clinic. The first trial here with Avastin was announced negative on March 12th, presented at ASCO; it prolonged the time to progression but it unfortunately did not prolong survival. Carbazitaxel is positive and now FDA approved. Abiraterone: the interim is complete and we will get more results later this year.

Here is an overview of new hormonal therapies, new chemotherapy, new immunotherapy, and then a brief mention of what are called stromal targeted therapies. Abiraterone: when we go back to the synthesis of testosterone which I was showing earlier, there are a series of enzymes that it takes to get to testosterone; the agent shuts down synthesis of this enzyme and thus you cannot make testosterone. It appears that

you may be switching off the synthesis of testosterone in the cancer cell. This drug had been sitting on the shelf for a very long time and finally was pulled off the shelf by Johann Debono, who was instrumental in getting this agent into the clinic. These are PSA declines, which are dramatic with abiraterone. These patients who had been treated with chemo and failed chemo, and the vast majority of patients had substantial PSA decline.

This is another hormonal compound called MDV3100 [phonetic] made by Medovation [phonetic]. Charles Sawyers [phonetic], in California at the time, now at Memorial Sloan-Kettering in New York, put this deal together; with his chemist, he created a compound that would bind to the androgen receptor very tightly, eightfold better than the best we have today. They looked at this in humans and found there was dramatic PSA declines even at their lowest doses on their phase 1. They published recently in Lancet. It made no difference whether the patient had prior chemo, the cancer cells remain hormonally sensitive. It turns out that if you are going to manipulate the androgen receptor, you are going to affect PSA disproportionately to tumor volume; the PSA gene can get turned off more than the tumor volume shrinks, because the PSA gene has what we call an androgen response element. We have yet to get all these final survival results, and we must be careful because when we stop these agents, the tumor can actually grow faster.

Moving on to carbazitaxel, the new FDA approved agent, which is a semisynthetic taxane derived from a Taxotere type base, was just as good in the preclinical data as docetaxel in sensitive cell lines, but in tumor cell lines that were resistant to currently available taxanes, this agent was still active. In the phase 1 trial, they noticed antitumor in metastatic cancer resistant prostate cancer patients including those patients that were docetaxel resistant. We put together a big trial on which myself and Johann Debono were co-principle investigators. These patients had progression despite previously being treated with Taxotere. The trial was big: 146 sites, 26 countries, 755 patients, and mitoxantrone was used in the control arm. Primary endpoint was overall survival.

Subjects had to have documented progression in order to get onto the trial, and you had to be treated with a minimum of at least 225 mg/m^2, no prior treatment with mitoxantrone, good performance status, and good organ function. Medium PSA was 127, 143; the majority of patients had measurable disease; the vast majority had bone disease, but visceral disease was almost 25%, which is the highest percentage of visceral disease of any trial I have ever seen. These patients were advanced: they had already had hormones and failed; they had chemotherapy and failed. As it turned out, they often had not just one chemotherapy; about 30% of the time, they had had more than one chemotherapy before they came in. About 70% had had one type of prior chemotherapy; the other 30% had already received two or more. These are tough patients. In the control arm, your median survival was about 12.7; in the carbazitaxel arm, it was 15.1 months.

Is median important? Yes, it is because that is what it is statistically. Is prolongation in survival statistically significant? Absolutely; it has got a great P value. Is it clinically significant? I think so. Unfortunately, quality of life studies were not done for this study, but will be done moving forward.

This is an area of unmet need. Nobody had ever shown a prolongation in survival in these patients before; this is the first and only trial to have been reported with a survival benefit in this setting.

Here are some interesting subanalyses. The hazard ratio, which measures the rate of death as a function of time, looking at the risk over time with lower being better, this is 0.59 in North America. The risk reduction of death during the time period of the study was 41%, which is very good. This is better than Taxotere at 0.8. This is 0.7 which is the best hazard ratio ever reported in advanced prostate cancer. Another interesting finding was the patient who responded initially to chemotherapy, then progressed, and then went on carbazitaxel, did really well when compared to the mitoxantrone group.

Secondary endpoints included PSA assessment, tumor assessment, and pain assessment. The response rate by PSA was double that of mitoxantrone, 39 versus 17.8; median time to progression for PSA was 6.4 versus 3.1 months, which was about doubled for PSA progression. Tumor assessments and pain assessments, which are minority, these are highly sensored events, and consequently, their confidence intervals are very large and it is hard to know exactly what to do. I will say the tumor assessment favored the carbazitaxel; the pain was the same as mitoxantrone.

Exposure was higher in the carbazitaxel arm, and full dose level was administered to about 90% on the carbazitaxel arm, which means that the average patient got about 90% of the intended dose. In terms of cycle delays, less than 10% of people had cycle delays. There had been some criticism over the dose saying it might be too high; I think it was about right for about 90% and too high for about 10%.

There were some pretty serious side effects here. Febrile neutropenia was 7.5%; this is double that of Taxotere. This may be due to not just the drug but because these patients have very advanced disease. Even on the mitoxantrone, 46% of subjects had diarrhea, with 6.2% having pretty serious diarrhea.

These are the counts: if we look at mitoxantrone, we see neutropenia occurs in 58% of the patients in this trial, but in the TAX327, the frontline trial, same dose and grading system, neutropenia was only 22%. A lot of this suppression is due to the fact that the patients were heavily pretreated.

Deaths occurred, including toxic deaths. Adverse event deaths was 4.9%, which is really high but is not equally distributed geographically. In North America, the death rate was 0.9%, essentially the same as mitoxantrone. In Europe, the death rate was higher but included Eastern European countries; in India, there was a very high rate of toxic deaths, including three deaths at one site which got shut down. Your doctor matters, and how you are managed matters. This drug is an important and effective drug, it fulfills an unmet need, but has a safety profile that demands meticulous attention to detail. In particular, careful management of neutropenia and diarrhea. This agent should be reserved for people with metastatic castrate resistant disease with progressive disease post-docetaxel and a good performance status and good organ function; this should not be used in people on their death bed.

This trial looked at immune based therapies. This trial was done in mice and published in 1993. A gene called GMCSF was put into the mice and rendered the animals tumor-free.

Some researchers at Dendrion [phonetic] combined this agent with prostatic acid phosphatase, which is secreted by prostate cells, including cancer. They took white cells which stimulated the immune system from the patient, isolated the antigen presenting cells which help stimulate the immune system, exposed them to this new antigen that is a fusion protein, loaded them up with a bunch of other cytokines, and stimulated the immune system. Sounds pretty farfetched, yet actually, in small randomized trials, it worked, and in a big randomized trial, it also worked. Reimbursement is controversial and remains yet to be determined.

Looking at stromal targeted therapy, there is a rapid autopsy program at Michigan from which tumors from patients were obtained, and which showed that the prostate cancer could look differently depending on what part of the body the sample was taken, and when analyzed genetically, it could have different genetic markers, even in the same person. When you went to the next person, it got even more different and thus confusing. As we move forward, we need to consider heterogeneity of the disease because unfortunately, nothing we do today will cure advancement of prostate cancer.

The cancer stem cell has nothing to do with an embryo but rather is the stem cell in cancer. When we give hormonal therapy, we get great responses, and then the tumor comes back; occasionally with chemotherapy, we get good responses, and then the tumor comes back. We believe that there is some stem cell down here that does not even make PSA but can renew itself and put off these progenitors. Certain diseases like chronic myelogenous leukemia have a single mutation which you can hit with dasatinib and really make a difference, but nevertheless, these patients still have trouble with resistance. The problem we face today is the dual challenge of advanced prostate cancer, comprised of the heterogeneity in the stem cells: how do we target cancers that are heterogeneous in both genotype and phenotype in the same patient? How do we kill a stem cell in patients with widespread cancer?

One thing that has arisen is defining the interactions between the stroma, the supportive environment, and cancer cells. There is a definition of ecologic niches which can support cancer growth. Prostate cancer goes to bone; something about the bone allows growth, something about the kidney, for example, does not. Just as we may destroy the forest habitat where a bird lives, thereby making the bird go away, we can use the same idea to make cancer go away. These stromal targeted therapies use antiangiogenesis inhibitors, such as Avastin, which unfortunately did not get a survival benefit despite some positive results, and sunitinib, thalidomide, and lenalidomide.

Bone and tumor targeting agents, the endothelin antagonists, are probably not enough in and of themselves to affect prostate cancer cells; we will find out with docetaxel combinations. Dasatinib is another agent which inhibits the Gleevec type target in myelogenous leukemia, but also inhibits a compound called SARC [phonetic], an enzyme that is very active in advanced prostate cancer. And bone stromal targeted pharmaceuticals, including the radium-223 which I find exciting.

Where do we go from here? Even for our curable malignancies, it takes four drugs. Hodgkin's disease, non-Hodgkin's lymphoma: it will take a multiplicity of drugs to be able to move this field really forward. We are playing around the edges; we have not really begun to put these together in combination, and this is one of the challenges that

we must do. We initially had trouble finding the drugs; now that we have a few more drugs, we have got to start putting them together correctly. Maybe we need to take multitargeted therapy and not only target the tumor but maybe add in some strategic environmental sites. If we ever figure out how to kill a stem cell, then the whole game changes.

Male Participant

Looking at the five agents you spoke about, what is the risk-benefit, and how do I decide which one of those agents I should use if I have got advanced disease?

Dr. Sartor

You have to look at the risk-benefit for each agent. There is a hierarchy of toxicity. Generally, what I use are the least toxic agents first, namely, the secondary hormones and will take these as far as I can go. Following that, I typically go to the chemo. With the new immune agents, we might be able to alter that paradigm as soon as we work out all the payment details. Something like carbazitaxel will be the caboose; that will be toward the end. Think about it in terms of toxicity: we want to do the least toxic first, and then we kind of reserve because right now, nothing is a home run. I am very supportive of clinical trials; the idea is always to try to do better tomorrow than we do today.

In response to an audience question, the kinetics of tumor growth are very important. There are two issues: the kinetics and the volume of tumors that I pay attention to. Regarding kinetics, I am still prone to use my secondary hormones first, but I know that if I fail my first secondary hormone in a short period, that I am unlikely to get good benefits from another one. In that case, I alter my usual sequence and I bring the chemotherapy upfront. I have a menu from which I choose what I think is right for the patient at that particular time.

Male Participant

The immunotherapy is very exciting. How do you design a study that combines it with chemotherapy?

Dr. Sartor

We have a bit of yin and yang here. On one hand, we need the immune system to have the effects on the tumor that the immune therapy, we hope, is going to promote; on the other hand, the chemotherapies are going to inhibit the immune system. So this seems like an opposite, but they are opportunities. One way to augment the effects of immunotherapy is through using radiation. If you radiate a tumor, you expose more antigens and do not down-regulate the immune system substantially because you can target your radiation. There is good data from animal models to show that radiation up-regulates the immune response; maybe what we need to do is use radium-223 combo. Chemotherapy may be a challenge, but some of the others may not be.

In response to an audience question on cost, I do not believe the price will come down with Dendrion. Personally, I think it will be competitive market pressures which change the price, not Dendrion.

Male Participant

Does hormone manipulation reduce the prostate cancer? And does the scrotum cause the cancer?

Dr. Sartor

Hormone therapy does reduce the prostate cancer in size; you take a big tumor and you shrink it down. But it does not make the tumor go away forever; you do not cure people with hormonal therapy. Caveat: when you use radiation plus hormones, you cure more people than when you use radiation alone, but if you wait until the disease has spread and use hormones then, those people are not cured. That is the problem with the stem cell that keeps coming back despite our best efforts.

The other question regarding does the testosterone cause the cancer, we know if we manipulate the hormonal environment with drugs like dutasteride and finasteride, which do not actually change testosterone, they change its more potent brother called dihydrotestosterone, you can reduce the incidence of the common cancers, the Gleason six cancers, by about 25%, 30%, but on the high grade cancers, the Gleason eight, nine, ten, it does not work. You might be able to inhibit the cancers which you do not care about, but you do not inhibit the cancers which you care about most.

Male Participant

Is there a push to move the new therapies up sooner in the disease spectrum so that the patients are not marinated already with androgen deprivation therapy and docetaxel, to see whether it is going to be more effective before it builds resistance?

Dr. Sartor

Yes. Let's take hormonal therapy in its old form, and then in its new form. People are already moving the abiraterone up in clinical trials in the neoadjuvant setting pre-prostatectomy, and there is a move afoot for a large abiraterone trial using a shorter course of abiraterone than usual LHRH analogues in the neoadjuvant/adjuvant setting in combination with radiation therapy. Trying to move the agent in the very upfront setting has a tremendous regulatory hurdle because drugs are approved today because they make people live longer, and if you do not make people live longer, it is hard to get the drug approved. As well, the payoff may be 15 years away; it is financially unfeasible. Companies are concentrated in this late stage space not because they really want to be there, and not because patients want to be there, it is because if you are an investor and you want to get your money back, you have got to go late in order to get approved, cynical but true.

In response to an audience question regarding the cyber knife, the interesting thing about the newer technology is you really have to wait long-term to figure out how well it is going to work. A lot of the technologies look promising in the short-term, over the one-year period. But for prostate cancer, particularly localized disease, you have to follow people for a long time to figure out what works. Side effects present another hurdle with the cyber knife long-term. I am conservative in early stage disease.

Mr. Simons

Combination therapy carries with it side effects resulting from treatment. How do we deal with this?

Dr. Sartor

There are a lot of challenges with combinations, including the additive toxicity. The process will be trial and error. Even though we are smart when it comes to biology, we still must be empirical because our ability to predict is imperfect, and that leaves us requiring we get the data. My hope is we will have more active agents that are non-chemotherapeutic, and those combinations will flow a little bit easier. There is a tremendous intellectual challenge in drawing new agents from different companies together.