Current Trends in the Management of Advanced and Late Stage Prostate Cancer with Dr. Maha Hussain

When should patients start asking about involving an oncologist in their care, how can we manage quality of life issues while being treated for advanced, metastatic, and castration-resistant prostate cancer? We are discussing how to manage advanced and late stage prostate cancer with **Dr Maha Hussain** and panelists. The panel will also be touching upon the results of important clinical trials from the GU oncology meeting. Our prostate cancer talks are conducted in association with Prostate Cancer International and Prostate Cancer Foundation.

Full Transcript:

Priya Menon : Hello, everyone. Welcome to Cure Talk. I am Priya Menon, Scientific Media Editor at Cure Talk, joining you from India; and I welcome all of you this evening to a discussion on prostate cancer. This is Cure Talk's 83rd episode, and all our prostate cancer talks are conducted in association with Prostate Cancer International and Prostate Cancer Foundation. When should patients start asking about involving a medical oncologist in their care? What do patients need to know that can help them optimize and not just the extent of their life but the quality of that life while being treated for advanced metastatic and castration-resistant prostate cancer? We are discussing current trends in the management of advanced and late-stage prostate cancer with a very distinguished prostate cancer expert, Dr. Maha Hussain from University of Michigan. Dr. Hussain is an internationally renowned clinical researcher and an expert in genitourinary malignancies, particularly prostate and bladder cancer. Welcome to Cure Talk, Dr. Hussain.

Dr. Maha Hussain : Thank you for the opportunity.

Priya Menon : My co-host for the show is Mike Scott. Mike is Co-Founder and President of Prostate Cancer International, a prostate cancer-specific, not-for-profit educational and informational organization based in Virginia. Supporting Dr. Hussain and Mike on the panel are experienced and knowledgeable prostate cancer survivors and caregivers – Tony Crispino, Jan Manarite, and Richard Davis. I extend a hearty welcome to the panelists and to all our listeners. Towards the end of the discussion, we will be addressing questions sent in by the listeners. If you have a question for Dr. Hussain, please press 1 on your keypad and we will bring you on air to ask your question. With that, I will now hand over to Mike to begin with the discussion. Mike, you are on.

Mike Scott : Thank you, Priya. I appreciate the introduction and good evening, Dr. Hussain. Thank you very much for taking the time to join us.

Dr. Maha Hussain : Thank you for the opportunity. Its my pleasure.

Mike Scott : Not at all. As Priya had…, had indicated, what we are interested in hearing from you this evening is…, is when do you think patients should start to involve medical oncologists in their treatment and I…, I recognize that you may have a slightly different perspective from some of the urology community. Also, you need to talk about what patients can do to maximize the quality of life as well as the extent of that life because clearly patients can be on treatment for advanced prostate cancer, not just for months but for many years and…, and the quality of their life is therefore very important over a considerable period of time. So, with that, I will hand over to you to talk about the things that are of great interest to you in that area and also some of the new learnings that you may have come up with after the genitourinary cancer meeting that was completed recently.

Dr. Maha Hussain : Absolutely. Thank you very much, Mike, and its really a pleasure to be…, to be here. So, let me begin with the issue of when to start involving a medical oncologist in the…, in the process of care and in the process of helping with the decision making for the patients. I am going to probably begin by saying that first of all, I am medical oncologist, so my views are…, could be interpreted as biased; however, I do think that there is room for a medical oncologists' opinion at every step in the process, starting from diagnosis of a cancer that is not irrelevant type of cancer. So, to give you an example, I recently saw a gentleman who is 58, who has prostate cancer at Gleason 7. He has no other health issues, and he saw a medical…, I am sorry, a radiation oncologist and he saw a surgeon and he obviously got two different opinions. So, while they told him you have an excellent chance of cure, you are treatable, each person preferred one treatment over the other. This is when he decided to come to see a medical oncologist for the discussion. I certainly would argue that patients who have high-risk local disease, so bulky disease in the prostate or a high Gleason score where there is the issue of balancing the local…, local, regional, and systemic control, I do believe that medical oncologists should be involved in helping the patients with their decisions going over what we know and what…, what is the data from, you know, well done clinical trials and so on. So, that would be from one end of the…, of the spectrum. Is it a must at that level? Not necessarily but I do think it could be helpful. I do think that when patients with prostate cancer have relapsed after local treatment with either a rising PSA and no evidence of obvious cancer spread by scans or subsequently who develop metastatic disease or those who right now have new metastatic disease, I do think they should consult with medical oncologist and partly because the options of treatments can be quite different nowadays and we can talk about that perhaps later and there are issues with the appropriate amount of imaging, what is the appropriate treatment if one has just the rising PSA versus real metastatic disease? If a person has metastatic disease, do they have options of clinical trials and…, and, you know, should they be considering chemotherapy early versus not and so on. I also think that there are a fair number of patients who are treated primarily by the urologist who, for whatever reason, are on hormone treatment and now have disease progression, either by PSA going up or by cancer getting worse on the scan. This is really an area where I do believe that they are, in my opinion, better off with medical oncology because of the potential options coming to them and the different management issues that are going to be necessary and this kind of ties nicely, Mike, with the second question, which is the quality of life and, as you know, quality of life is different for each person. What might be bothersome for one person is not at all bothersome to another person and depending on the disease setting, the bother becomes relative. So, someone who has no symptoms whatsoever from their disease, let's say just the rising PSA, and somehow ends up on hormone treatment, that treatment can cause more bother than someone who has metastatic disease, not because its physically that much different, its because the context is different and the quality of life has to be looked at together within the context of risk and benefit from treatments and so on. I do think that from a patient perspective, the best quality of life can be made by better understanding of why someone is needing the treatment so they can basically balance and understand the risks and benefits from what the decision that they are going to make with their…, jointly with their physician regarding the treatment, also understanding the objectives from the treatment and also trying proactively as much as possible to maintain a relatively, as much as possible, healthy lifestyle so that it can balance the potential downsides of different treatments that might be prescribed for them. I also think that it is very important for the patients to be proactive in asking their physicians about what they may have in terms of services available at the institution or locally to help with different issues that might surface as it relates to the treatment. There is the other factor which is the, what we call the, survivorship factor. So, as you know, the vast majority of patients with prostate cancer are…, luckily nowadays, are diagnosed with localized disease which is highly curable…, I am sorry…, highly curable with local treatments. Those treatments do leave the patient with residual effects, whether its incontinence, whether its impotence or sort of radiation-related issues and things like that. So, most of the institutions and certainly at our place, we do have actually a specialized clinic that is the survivorship clinic which is focused on aspects of maintaining and maximizing quality of life for patients as it relates to their symptoms, whether its physical or mental, and I would say to my patients in general, do not hesitate to ask and do…, do not be embarrassed to request help in that regard. Now, one more thing I would say is that for patients who have advanced prostate cancer, that is metastatic or end-stage castration-resistant disease, we also have palliative care symptom management services available that can work with the managing physicians to try to optimize either the disease-related symptoms or side effects related to the cancer itself and again these services are available and they are both, what I call, mind and body-type focus services that can be instituted

and I do think that it makes a huge difference from the perspective of the everyday life of our patients.

Mike Scott : Thank you. That's very helpful. Now perhaps you would like to talk to us a little bit about any new data that you felt came out of the GU oncology meeting?

Dr. Maha Hussain : Oh, certainly! So, perhaps I can practice this by saying that research is what will cure cancer and in the business we are in, our…, our hope is ultimately to reach the metric of cure. In the process obviously, research is what's going to lead to the discovery of things that could help us either diagnose the cancer much earlier where we can now cure it with local treatments or discover different interventions, whether its medications, radiation, imaging, that will help us obviously control the cancer and prolong life and hopefully reduce that from the advanced prostate cancer. So, we just came back from…., and so from my perspective…, I am sorry, let me back off here. So, I do think I am very… I guess I would like to encourage patients when they are consulting with their doctors to ask about what clinical trial is available for me, doctor, and carefully consider the options and make a decision that's informed based on what is suitable for the patient's situation. Please ask all the time and look into possibilities because, as I tell my patients, every drug we have in the market today started as an experimental drug at some point and so I think that's very critical. I do think there are several very interesting things that I think we…, I came out with from our recent genitourinary ASCO meeting that happened in the last month. I do think one of the areas that are interesting is and we are getting a lot of focus on is improved imaging. As you know, when we diagnose cancer, one of the first steps in evaluating what we are going to…, how we are going to manage that…, that cancer, the first steps that we need to evaluate is how big is this cancer and where has it gone and so there is a fair amount of focus on imaging, whether its molecular imaging, MRI, PET-based imaging and so on and so one of the very interesting projects was reported as a preliminary, obviously very early phase, is looking at enhanced MRI imaging for lymph node staging and prostate cancer, which I felt was very interesting because clearly we know that prostate cancer when it spreads either goes through the blood vessels and settles in the bones that way or other organs or it goes through the lymphatic system and settles in the lymph nodes and so this is a technology that allows for a priori assessment potentially of the extent of the cancer prior to intervening with surgery or radiation so that better planning can be done. So, I said that was an interesting technology and a…, and a contrast, a special kind of contrast-enhanced agent that was being developed at the NCI.

Dr. Maha Hussain : Another thing that I thought was very interesting was, all of you must have heard and I don't know if you are familiar with the report that was…, that came out of the Hopkins group regarding the androgen receptor splice variant-7, which is… The androgen receptor is essentially the window or the door that is…, is…, that where the male hormone testosterone or the androgens will actually go into the cell through and trigger all kinds of stimulation of the cell to grow and divide and so we know that in patients with castration-resistant prostate cancer, which means they have already seen hormone treatment to suppress their testis from making the male hormone and where their cancer begins to grow, we know that we have, at least right now, two drugs that are still targeting the androgen pathway and the androgen receptor pathway, specifically abiraterone and enzalutamide. We know that if you take a 100 patients upfront, its about half roughly that will respond…, their cancers will respond to the treatment and so its been very peculiar as to why is it doesn't…, some cancers don't respond and what is it about these cancers that, you know, are not responding and can we predict who is not likely to respond so that we can spare them the physical and monetary cost of…, of these drugs and so the…, the group looks at this particular variant in the setting of patients undergoing abiraterone or enzalutamide and demonstrated that in a preliminary manner that those who express this particular alteration on the androgen receptor, they are not likely to respond to the hormonal agents. Interestingly, at the GU ASCO, Dr. Antonarakis reported that they looked at whether the patients who expressed this particular…., particular alteration, for short I am going to call it ARv7, whether they will respond to chemotherapy and interestingly it didn't matter. So, Taxotere or docetaxel in fact was not…, there was similar activity for docetaxel irrespective of what the AR variant status is, which I think is an important observation because we are all beginning to see that patients who had, let's say, abiraterone upfront seemed to not respond as well to enzalutamide afterwards and so on and this may be because of different resistant things that the cancer, you know, makes. At least in the setting of this particular variant, it doesn't appear to be prohibitive and it suggests perhaps that patients should not be delaying chemotherapy too much.

Dr. Maha Hussain : Another observation that I thought was very interesting is… As you know, the immune treatments are really very interesting treatments across multiple tumors and trying to help the body overcome the…, the effect of the…, overcome the…, the resistance to cancer by trying to arm its immune system to fight the cancer is an area of very, very exciting…, is going to a very exciting time and the checkpoint inhibitors, as we call them and you might have heard about the PD-L1-type agents, inhibitors are a very exciting research area and the issue is whether these types of agents and others that are trying to arm the immune system to fight the cancer are…, a going to somehow transform how we do things in prostate cancer or not and so there was a report on a trial that's looking at an immune agent called Prostvac and together with another agent called ipilimumab and the data from that one…, again these are very preliminary, I should caution everyone, very preliminary, but the data looks very, very interesting in terms of the efficacy and in terms of how long people lived when actually both treatments were combined together. So, I would say, stay tuned because in fact there are trials that are being planned in those areas. Another area that I felt was very interesting is the…, and this is unfortunately is…, and let me…, let me finish the good news. Another area that I felt was interesting is the fact that there was some preliminary data reported on the combination from an expansion or open access-type phase of a trial with radium where they looked at whether patients who, say, were on enzalutamide or abiraterone and got radium as part of the extended access, did they do well and, you know, was there any kind of bad signal, was it safe to do, and so on and so what's interesting is that there is a clear signal of safety and well tolerated type combination treatment and so the…, the preliminary data on outcomes also looks rather interesting and so, in fact, there are, I believe, now trials looking at combining these agents with the radium to see how…, how…, how that treatment is going to…, whether its going to result in improved outcomes overall and then finally, on the positive front and…, I want to mention that there are a slew of agents that are coming to the clinic in the form of clinical trials, looking at what I would call smarter hormonal pills, so to speak, and there was an interesting observation from a group based on pre-clinical work, so laboratory work on a drug called ODM-204 which is…, is one of those agents, it has the same kind of effect like abiraterone in some way in terms of how it works or the mechanism of action together with inhibiting the androgen receptor and so on. So, I would say stay tuned because more and more smarter hormonal drugs are going to come to be tested. Now, whether they are better than what we have right now remains to be seen, but I do think that some of them may turn out to be quite a bit better.

Dr. Maha Hussain : Now, finally, I want to end with a couple of notes and one of them is on a drug that is…, I have been involved in in working with in the early phases of it, is a drug called cabozantinib, a drug that we reported a couple of years ago based on observations from us and others suggesting a very promising level of anti-cancer effect. Unfortunately, this drug has gone into phase III trials and what's compared to prednisone and the trial…, phase III trials, these are trials that are generally quite large and they are looking at an outcome of survival. Does it prolong life? And, unfortunately, this drug failed in the population that was tested…, it was tested in, which is men with metastatic, castration-resistant prostate cancer. It failed to show a survival advantage, which highlights the importance of doing these types of trials and not jumping into conclusions from early phase-type trials, where there is a lot of promise. Promise is important, but its our obligation to prove that, in fact, we are helping patients and we are not subjecting them to harmful agents without an advantage with regard to survival. So, unfortunately, that…, that trial results were not positive for survival. There was some hint of activity and delay in cancer progression. And, finally, I want to make a comment and I don't know, I can combine it with my comments, Mike, on chemotherapy in patients with metastatic disease. This is the GU talk update. Do you prefer if I hold off right now or should we do that because I see a question possibly on the charted trial?

Mike Scott : Right. Let…, let…, let…, let me ask you a couple of questions and then maybe we can come back to that. On the very simplest level, obviously a lot of patients probably arrive in your office and they tell you that there are all sorts of supplements and things like that as well as the hormonal or chemotherapy. What do you say to patients who…, who come in with…, with, you know, a long list of supplements that…, that they are taking or other agents where we really have no good data that tells us one way or another whether there is a benefit?

Dr. Maha Hussain : And you are absolutely correct. I also… So, the supplement will take, I guess, two forms, is vitamins and then I am going to categorize the others under another category and what I would say is that

there is really no objective data today that taking supplements of any kind beyond a healthy balanced diet and perhaps basic things if you feel that your diet is not, you know, adequately supplementing you with, let's say, vitamin C or calcium or something, that there is no data today that says any of the supplements in fact had a positive influence on the cancer or the outcome from the treatment. I will also go one step beyond and point out that if anything, whenever we tested some of the vitamins like vitamin A or the supplements like selenium and others, there was in fact a harmful effect and so just because something is natural, it does not make it safe and I would caution patients especially because some of the drugs that are oral agents may actually interact. Either the supplements may cause something that will affect the drug in the body or vice versa, where the level of the drug may go to a low level such that it becomes, you know, not effective or may cause side effects. So, I would encourage patients to…, and I know there is all kinds of stuff on the internet. Just coz its in the internet, it doesn't make it the truth and just because somebody swears its true, it doesn't necessarily mean its true. It is not proven to be true. So, I would caution… I would caution the patients in general and I would encourage you very much to consult with your doctors, primary care and oncologist, regarding the safety and the wisdom in using some of these medications or, I am sorry, some of the supplements. I also remind patients that a lot of the chemotherapy we use, by the way, is natural product and so that doesn't necessarily mean its…, its safe and a lot of things that are poisonous to humans are also natural products. So, being careful is important.

Mike Scott : Thank you. So, now I have a rather more complex question and you might want to weave the answer for the charted trial into this. One of the things we saw… One of the things we saw from the charted trial was that you did not have to give prednisone along with the docetaxel and one of the things that I have been thinking about is that in most of the trials that we have been…, in fact I think all of the trials that we have been doing in late-stage cancer, prostate cancer, we are adding a new drug on top of standard hormonal therapy and I am seriously beginning to wonder whether that is always a good idea because while you are subjecting the patient to all the side effects of standard hormonal therapy in addition to the new drug that one is adding and yet as you kind of alluded to earlier on, the patients often may be getting more side effects from the hormonal therapy than they are any survival benefits and I am…, I am just curious how you as a researcher is starting to think about how we move forward with trials that may help to resolve some of these issues.

Dr. Maha Hussain : Mike, this is an excellent question and I have to tell you that it is complicated and so you are absolutely correct. I am not sure that we know from a biological perspective that what is the 100% correct answer. So, you are absolutely correct that in charted there was a cautious choice not to add prednisone on top of everything else aside from the use around, the need of steroids around the time of chemotherapy which is part of what we…, what is required from a safety perspective and you are absolutely correct that in the castration-resistant disease, people keep adding prednisone to…, or drugs to prednisone for example and to…, and therefore, when the drug makes it and it goes into FDA approval, it is packaged with prednisone. So, in this case, docetaxel or Taxotere is packaged with prednisone when given in castration-resistant disease. I am… I am going to give you my perspective and this is not necessarily evidence based but rather experience based. I do think that the disease context does matter and it matters at two levels, one of them from the efficacy perspective and then the other one is from the tolerance perspective. So, in patients with advanced castration-resistant disease, I would argue that the reason prednisone was given in addition to Taxotere is because when the…, when the trials were done, specifically the…, the sponsored trial, not the SWOG trial that I was part of, because the control arm had prednisone and you really didn't want to put your drug at a situation where you are going to lose. So, you wanted to make sure that the…, the arms are balanced with regard to, you know, the other drug included, in this case prednisone.

Dr. Maha Hussain : Now…, now I actually have a different perspective on it, in that biologically if you think about it, patients who have castration-resistant disease historically, before we got all these fancy drugs, actually were getting treated with steroids and biologically we know that the glucocorticoid receptor and the effect on the adrenal gland and so on, does result in anti-tumor effect in patients and we all have our maybe…, maybe not…, not huge number, but over the years we all have had our groups of patients who for whatever reason are responding to steroids, whether prednisone. Generally in my case, I use dexamethasone and I actually have patients use out with castration-resistant disease with response. So, I do

think that one thing we need to think about in this disease, that one size does not fit all and what we do in castration-resistant disease in terms of the regimen development does not have to be 100% mirror image in the hormone-sensitive disease. Hence, in the setting of the hormone-sensitive patients getting docetaxel or Taxotere for together with their hormone treatment, when you are talking about a disease that is not resistant and a disease that is very responsive to castration, that the mileage of pain from adding steroids may not be there as opposed to the other setting. The other thing I want to mention is that in settings where we have bigger, bulkier disease, while the steroids do have side effects, there is no question they do have some benefits that are…, may not be huge anti-cancer effects for every patient but rather energy, pain, appetite and so on. So, some of us actually resort to adding these medications selectively for some patients who may not be, let's say, on Taxotere or something like that and clearly with drugs like abiraterone, while people talk about it is safe to give without the prednisone, I will say from my, again anecdotal observations on my patients, abiraterone appears to be quite well tolerated and I wonder how much of that because of the prednisone being on board. So, I don't know if this is a long answer to a short question and I don't know if it answers your question.

Mike Scott : Well, it answered some of it and…, and obviously we are not…, we are not hoping to get perfect answers to everything tonight. At this point, what I would like to do is…, is open the…, the discussion to a couple of the other people on the panel and if I may, I am going to start with Ric Davis. So, Ric, perhaps you would like to reintroduce yourself very briefly and then get your questions. I do warn everybody that some time in about the next 15 minutes, I am going to want to open this up to the rest of the audience for their questions as well. So, if you could try and keep your questions brief, that would be helpful. Ric!

Richard Davis : Hi! Yeah. Hello, Mike. Hello, Dr. Hussain and Tony and Jan, the rest of the panel. I am an advocate and my particular interest is helping men with advanced disease and their caregivers and I have worked with…, with Mike and some of the people on the panel for quite a while. Let me get straight to the question. You earlier on, Dr. Hussain, referenced the ipilimumab and Prostvac study, which had some pretty remarkable results albeit early. I'd like you, if you would, to expand on your thoughts on the role of immunotherapy in prostate cancer treatment and in particular, I am aware from…, from working with two or three Asians who were treated at your center, that your institution doesn't favor sipuleucel-T or Provenge. I am wondering how that works into your thoughts on immunotherapy.

Dr. Maha Hussain : Sure. So… Thank you very much, Ric. I am going to begin by, first of all, saying that we are…, as a physician and as a…, as a researcher and as a doctor with lot of patients, my obligations are to my patients and I do think that…, and I would like to also highlight that I do believe that the immune system does have a potential role. It is yet to be proven in the context of the types of drugs we are talking about right now. So, I am not making a comment about sipuleucel but rather the GVAX and so on. I think the data looks very promising and I will tell you this, as I tell people too, I am old enough to have seen very promising things or be even harmful and so… I am sorry, I said GVAX, I meant Prostvac. So, I would say it is… I think the immune system is something that we need to harness. I think that its not simple and its very complicated. I also know that from, I deal with other cancers myself, specifically bladder cancer, and I certainly look at the literature in lung and renal cell and so on. There is no question that there are some tumors that are much more prone to immune system manipulation in terms of treatment as opposed to others. And so… Again, I think there is promise. I think its important to support these types of trials to see what it would…, you know, what would the final results be and I would encourage patients to consider being part of these trials as much as possible. I also keep an open mind about their value, but I fully agree with you and that's why I actually listed earlier on, that particular trial out of the GU ASCO as a very interesting and promising-type approach.

Dr. Maha Hussain : The sipuleucel situation, we actually… There is a group of us, we are six medical oncologists who deal with prostate cancer and when the sipuleucel came to the market, it was very clear that an infrastructure was necessary because, as you know, its not just a pharmacy-prescribed agent. You have to get the …, the…, the patient's sample sent and…, and so on and so an infrastructure was necessary to be developed and built and we have in the area multiple centers who have actually been participants in the sipuleucel trials and therefore had a priori established infrastructure. So, we actually did a sort of quitting our patients to see what the take rate is with our patients and surprisingly the take rate was not huge and I will

say that until today I have referred maybe two or three patients and this is probably about the average for our group. So, its not not believing, its more after discussions with our patients with regard to what's available in terms of options and…, and what can be done and so on and if a patient seeks or is interested, we make a point of referring them to a center locally, whether its Detroit or in the region, where they could get the sipuleucel treatments. I don't know if that answers your question.

Richard Davis : Thanks. Yes, thank you.

Mike Scott : And your second question, Ric?

Richard Davis : My second question, again you sort of touched on this, but the…, the recent research from the prostate cancer dream team was to…, and some other places, suggest that around maybe 30% of advanced prostate cancer morphs from being a sort of adenocarcinoma, hormone-sensitive cancer, to a form that much more acts and resembles and responds like small cell neuroendocrine disease. Now, right now, those folks are often times being treated with carboplatin together with docetaxel or Taxotere or sometimes cabazitaxel or Jevtana. I am wondering how you see this morphed disease being treated in the future and…, and what are the treatments currently available…, are currently in trial that might become available to help this significance section of men that seem to have this…, this strange form of prostate cancer?

Dr. Maha Hussain : Ah, this is an excellent question, Ric, and I would say there are varying opinions on these observations. So, we have actually… Let me begin by saying that adenocarcinoma can have what we call neuroendocrine differentiation, but its still a prostate cancer adenocarcinoma. So, cancers sometimes acquire features that are not necessarily going to impact on their response to conventional treatment and the only thing I want to clarify, that an adenocarcinoma does not have to be hormone responsive or hormone sensitive because your average prostate cancer that we treat when it metastasizes, it is still an adenocarcinoma, its just hormone resistant because it develops resistant mechanisms and its not necessarily neuroendocrine or small cell. The other distinction I want to make is that it is only for the small cell…, small cell carcinoma, so this is basically…, these are small round cells and that's why they call them small cell. They have no specific glandular differentiation and have certain features that are very characteristic…, characteristic to that cell type, which by the way most common area for it is in the lung, lung cancer. We see it with other diseases like bladder and so on. When the cells end up to become that way, its generally the very minority of times, its not at 30%, its an extreme, I say, few percentages and those are the patients we generally treat like we treat this sort of the lung cancer with a platinum plus etoposide-type thing or taxane. The difficulty I think that we are having to deal with is exactly in the whole…, in the category of non-small cell but an adenocarcinoma that has significant neuroendocrine features to it and in that regard, I am not sure that we have enough data that says these are the patients that should be treated differently than what you normally treat. I should point out also that the…, we do have also a Stand Up To Cancer East Coast Dream Team, which Michigan is the lead institution, and I do not believe we see in that high rates of histology and in parts I wonder if its because of the…, the sample of the patients you are referring to are patients who have already been through two layers of hormonal agents, I believe abiraterone and enzalutamide. So, I do think that its a very interesting observation. For the small cell, there is no question, we use a different type of chemo and hormones are not the way to go nor is average…, the average prostate cancer chemotherapy. I would say for anything less than that, I…, I cannot tell you that I am convinced that I have seen any data that said they should be treated any differently right now. Now, there are agents that are being evaluated for neuroendocrine-type tumors and I believe there was one trial that was being planned or is ongoing right now, but short of that, I am not aware of any trials in prostate cancer for this particular histology or differentiation.

Richard Davis : So, just a quick throw. What hope can you give to men that…, that a phased…, who are not responding to abiraterone, not responding to enzalutamide? What is in the pipeline for those men?

Dr. Maha Hussain : Oh, so… So, I would say several things and let me begin by pointing out that clearly not responding to abiraterone and enzalutamide does not take hope away in that you have actually cabazitaxel and docetaxel as very active agents in…, in prostate cancer, by no means the cure, but certainly they can

work in these settings. They also have radium, Xofigo, radium-223, particularly if the bulk of their cancer is predominantly in the bone. So, there is no question that there are treatment choices that are standard of care and that just because the cancer is not responding to abiraterone or enzalutamide, that's not the end of the…, the end of hope. There are plenty of other drugs and we have seen these drugs work for these patients. There are different clinical trials that are being planned or are in the…, in the process of being activated, some of them looking at more novel agents, specifically as I mentioned, androgen signaling-type drugs. Some are looking at other relevant pathways where… So, one thing I should say, prostate cancer is a very smart cancer and the more your squeeze it, the more it develops resistance and begins to adapt and so there are different drugs targeting certain pathways like the PTEN, the PI3-kinase pathway, the CDK-46 which is cell cycle regulation and so on and a lot of combination-type trials are being planned. So, I would say there are plenty of trials going. This has never been… This has been an unprecedented era when it comes to clinical research and clinical trials in prostate cancer and that's why I think patients should ask their doctors and can actually look around on the clinical trials for what might be available. The language is very much lay language, should not be too complicated for the patients and they should look at that and see if there is something nearby for them, but certainly their doctor should be their resource, plus right now the internet has all kinds of resources for different cancer centers across the country for the type of trials available.

Mike Scott : Thank you, Dr. Hussain, and so with that we will go over…, over to the patient advocate par excellence, Jan Manarite. Jan, do you have a question for Dr. Hussain?

Jan Manarite : Umm… Yeah. As you are speaking, Dr. Hussain, I am thinking a lot about patients who are probably listening and I like to say that we are in an age of shared decision making. So, we need to share the language and share the information. So, there are a few things in the terminology, I think I might want to mention, that might be helpful, and one is that… and we tell our callers this all the time on the PCI helpline is that every drug has two names. So, as we are talking about these drugs, we are using the generic names, so it may be a little confusing for them. So, abiraterone is the generic for Zytiga, radium-223 is the generic for Xofigo, and so on. So…

Dr. Maha Hussain : Xtandi… Xtandi for enzalutamide.

Jan Manarite : Right. So just reminding that every drug has two names to the people listening and that can help in your research. I also get very excited when I hear you talking about patients making their own treatment decisions or treatment decision with their physician once they understand the risks and understand the benefits because that's a…, a great way to look at every treatment decision. I often have people make two columns on a piece of paper and write down risk and benefit, but that being said, I do find that patients have to speak up more about the risk column, which is primarily side effects and that's the place where they can be the most effective in the conversation with the doctor. So, I like to encourage them to do that.

Dr. Maha Hussain : And I actually echo your comments 100%. What we do in general and that's what I recommend to patients, in 99% of times, the decision doesn't have to happen instantaneously, meaning on the spot, and what I find the most helpful in terms of the shared decision making is that not to necessarily always make that decision when the patient is sitting with you in the clinic as we talk about things. We try to give them material ahead of time and there are plenty of resources available for the patients, but we certainly…, its our obligation to provide them what we feel is the most appropriate sort of profile for the agents we are talking about or whether something else we are doing and that I am talking about standard of care treatments so that they can actually think about it, look at, you know…, look at it and there are times where patients are eligible for more than one thing and the question comes up is, you know, what is…, what is the preference and, you know, patient will say, doc, you decide, and I'll say, no, we'll decide together and so I generally give them the material to think about, to take it home, reflect on it, to talk to their family or spouse or, you know, if they want to and what I find actually that in literally, I am going to say, 99% of times it may be, but over 95% of the times patients will come back and they have a much clearer understanding and much clearer idea of what they really want to do themselves.

Jan Manarite : Right and in addition, I sometimes encourage our callers to talk to the nurse about side effects in addition to the doctor. Sometimes that can be very helpful.

Dr. Maha Hussain : Absolutely.

Jan Manarite : And one more quick question… One more comment, one more question, I promise I'll be quick. In the clinic when the patient is talking to the doctor, I think its helpful for them to know that when the doctor is using the word "symptoms" or "symptomatic," they are probably just referring to pain or most of the time referring to pain. So, its important for men to have discussions about their pain because it can make them eligible or ineligible for certain treatments, so that discussion is really important.

Dr. Maha Hussain : Absolutely and I would say that I would imagine the vast majority of patients who are now being evaluated, when they enter the clinic there is a review of systems form that the patients are asked to go through and circle symptoms. This is extremely important to be filled because this is how it will help the physician, you know.,… Part of my…, my thing is I look at it, but I go over each one of these things that the patients have circled because there are times when the doctor walks into the room, all of a sudden the patient forgets lots of things and the conversation changes, when in reality I think its very critical to be very…, very focused on what are the current symptoms, what is the extent of it and, you know, what needs to be done to manage these symptoms and that would hopefully optimize the quality of life.

Mike Scott : So, perhaps we could have one quick question, Tony. I am sure you have had plenty uncut chances to talk to Dr. Hussain before.

Tony Crispino : I have had chances to do that. Hello, Dr. Maha. Its great to hear you here. I had a couple of questions. I am going to go ahead and just zip right on into it quickly. In doing that patient advocate work over at SWOG, we have a lot of discussion going on about what we are going to be doing with the future. You gave a rousing speech over at ASCO couple years ago and you are 20 years in treating prostate cancer, which I posted on my website. Its absolutely a terrific presentation you did with that, but I want to take it around and look up to the next 20 years. Drug sequencing and translational research, genetic expression, things like that we are finding that are exciting are not there right now and identifying genes in prostate cancer and maybe it may affect drug sequencing or treatment opportunities into the future.

Dr. Maha Hussain : Tony, this is absolutely on the mark and I think that… I just came in from a…, an international consensus meeting and I am going to put it on your radar screen for 2017. It happened in Switzerland in St. Gallen which is sort of an area where they used to actually do breast cancer consensus meetings for a long time and now prostate cancer has also arrived to the scene where there were international experts with the intent of discussing all of these issues of difficulties in the decision making and…, and the drug sequencing and so on and so forth, but I do think that science is actually teaching us a lot and let me give you my personal perspective and it may seem a bit radical, but I do think that it is possible. I actually view that the ultimate benchmark for success is cure and we know that we have done that with testis cancer. Testis cancer, when it spreads it is curable and its curable not by one drug or two drugs, its curable by multiple, sort of a multi…, multi-drug strategy plus potential for radiation or…, or… I am sorry, surgery and so on. So, I do think that in prostate cancer we need to be very mindful of the fact that the tumor sequencing or, as I say, the genetic analysis of the cancer, whether its the east coast or the west coast dream teams are doing, its extremely informative with regard to the heterogeneity of this cancer. We have actual genetics or a molecular or sequencing tumor board at University of Michigan where our patients were undergoing a biopsy. There, the tumor sequence is presented to look at, you know, what are the mutations and the other molecular alterations and so on and for some patients, its amazing how the cancer is complex and for others, it doesn't have that much, yet its incredibly resistant. So, there is a lot that we don't know, but I do think that there is a lot that we know nowadays and so if you use my benchmark of saying that the ultimate goal is to cure prostate cancer and short of cure is to prevent it from becoming castration resistant since we are talking about metastatic disease, I would say the space where we need to be is really in the hormone-sensitive disease space. This is where we can actually maximize the kill based on what we have today and the fact that the cancer was smart, it is not as smart yet, meaning has not developed resistance mechanisms like

more advanced end-stage disease and I would say that there are the data that we have on, say, the charted trial with the use of docetaxel or Taxotere with hormone treatment is certainly instructive. Its not cure, but certainly the amount of benefit with the combination which as you know is…, this is the trial that was done by ECOG and SWOG. It shows really that, in fact, the door is quite open to test the concept of maximizing treatment in that disease setting. I also think that there are different trials that are being planned or are going to happen where they are looking at, what I call, a multi-targeted strategy. Remember no one cancer is one molecular alteration and so its very critical that we lobby as physicians and as patients and as researchers that our trials need to be smarter clinical trials. Not looking at one thing, one alteration but rather look at a multi-targeted strategy because the ultimate goal is to kill the cancer cell. So, I don't know, Tony, if that answers your question, but I do…, I feel very passionately about the subject.

Mike Scott : Oh, we have a couple of minutes left and we may be able to get a couple of questions in from the wider audience, Dr. Hussain. So, I am going to hand this back over to Priya and see if we have a couple of those questions. Priya!

Priya Menon : Thank you, Mike. Listeners, if you have a question for our expert, you can press 1 on your keypad and we can bring you live on air to ask your question. (Pause) We have a caller on line. Person calling in from 730-6613, please ask your question. (Pause) Listener calling in from 730-6613, please ask your question.

Caller : – Hello.

Priya Menon : Caller, calling in from… Yes, you are live. Please ask your question.

Caller : Yes, thank you. Hi, Dr. Hussain. This is Dominic Morissi. You mentioned the excitement around some of the improved imaging and as a patient that's been recurrent and has advanced disease, it always befuddles me why some of this technology like some more dense PET scans aren't in more…, more prevalent use. We seem to be stuck on, you know, using old bone scan tech-99 technology and…, and…, and CT scans. Why… Do you think there is going to be faster adoption of PET scans in some of these…, some of the this advanced…, these more advanced tracers that are more meaningful for prostate cancer?

Dr. Maha Hussain : Thank you for the question and actually its an excellent question. In fact, this was one topic of discussion again at our consensus meeting recently. I think the biggest difficulties are…, is the…, the issue of trying to understand what that scan means. Remember prostate cancer or any cancer can circulate into the blood, settle in organs, but may never ever show its…, its face. So, finding it very early in 100% of patients is fantastic. The question is in which patient this particular seed is going to be relevant and I think that is part of the difficulty we are all struggling with when it comes to the MRIs or the PET CTs and so on is what does that uptake in a lymph node actually mean. Is it really going to be a relevant or irrelevant cancer? I do think ultimately the obligation is on the…, the…, the researchers and the medical community in terms of trying to define the, what I would call, the clinical utility of these tests and then make a decision. Part of the comfort we have, and I am going to count myself there, the comfort we have with regular CAT scan and bone scan is we actually understand what it means and when I see a lesion, its real. Its not a… Its not a fake thing or its not something that's irrelevant and I think that's part of the difficulty you are seeing. I do think that what we need to do as a, I suppose, country in so many ways, that our process for approving technology has to be tied into what is going to help us make decision, whether its going to help us make a decision or not and right now, the way we approve tests and…, and imaging and so on or even blood test, its based on a certain criteria. When it hits the clinic, the doctors are looking at it and say, I am not really sure what I am supposed to do with this. Does that kind of answer some of the questions you are addressing? I do think, however, that improved imaging is absolutely critical. The question is if not, can you pick it up? If can you pick it up and do you know that this is actually a relevant finding?

Caller : Thank you, doctor. I have… I have heard part of that discussion before, so at least my doctor is singing the same song. You have to understand what you are looking at and understand the relevancy. Thank you.

Priya Menon : Thank you, Dominic. Caller using (910)667-2141, please ask your question. (Pause) I guess we can actually look at some of the questions that have been submitted, Dr. Hussain. Maybe we can just…, couple of them because I think we are nearing the end of the show time. The first one will be, could you discuss any promising research in treatment being done for men who are diagnosed with Gleason 8 to 10 but with low PSA scores?

Dr. Maha Hussain : I think that from the perspective of treatment, I don't necessarily think the PSA by itself is the major driver and certainly there are trials that are being planned to look at…, certainly if its radiation-type trials at adding some of the most promising new hormonal agents into early…, early in the course of the treatment which is what I have talked about, to try to maximize the chance of cure. The other research we are seeing is to try to predict which Gleason 8 to 10 is going to result in a cancer spread versus not and so some of the work is looking at, what I call, circulating biomarkers in the blood. I do think its very…, very intriguing, very interesting, but very early in the course of the disease.

Priya Menon : Thank you, doctor. One last one. Recently, there has been info on using tetanus shots to spur a new system in controlling brain cancer. Is there to play…, try this try this on advanced prostate cancer patients with mets?

Dr. Maha Hussain : I am not sure that this is going to happen right now in prostate cancer. I think we have other promising immune strategies and I think that is which we touched base on them earlier on and I think that's probably going to be the focus for the next few years.

Priya Menon : Dr. Hussain, thank you so very much for being with us today. It has been wonderful listening to you. Mike, Jan, Tony, and Ric, thanks a lot for the active participation. We have come to the end of our one hour, and the talk and the transcript will be made available on Cure Talk's website. Please visit curetalk.com for details on our upcoming talks and searching…, and for searching for prostate cancer trials, please visit award-winning tooltrialx@trialx.com. Thank you, everyone.

Jan Manarite : Thank you.

Mike Scott : Thank you, Dr. Hussain. Good night.

Dr. Maha Hussain : Thank you.

Tony Crispino : Bye.

Dr. Maha Hussain : Bye.