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Contents

Session 4: The Future of Castration-Resistant Prostate Cancer: Part 1 – Raoul S. Concepcion, MD

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Summary of Previous Day's Discussions

E. DAVID CRAWFORD, MD: Good afternoon everybody. Let's go ahead and get started. We welcome all of the new folks that are here. We have been rotating people in and out and so who's new today that wasn't here yesterday? Raise their hand. Adrian, you're new. Come on and raise your, okay. Just let's have everybody introduce themselves, the trio back there. We'll get a mic for you.

ADRIAN GOODALL: Hi, I'm Adrian Goodall. I'm the brand lead for the solid tumor portfolio at Sanofi with a focus on Jevtana for prostate cancer.

DR. CRAWFORD: Okay. Who else is new?

JOSEPH GERMINO, MD, PHD: Joe Germino from Bayer, U.S. Medical Affairs.

DR. CRAWFORD: What do you do?

DR. GERMINO: I don't know.

DR. CRAWFORD: You've been around a long time. Anybody else new? Okay. Old? Okay. So we have an exciting program here this afternoon. Just a reminder that our group dinner and libation will be tonight. We usually have a lot of fun doing that, 7:00 p.m. in the Lakeside Terrace which is, where is that? Across the way?

MALE VOICE: Near the golf shop.

MALE VOICE: Yeah, mezzanine level, mezzanine level of the main building, and we'll have cocktails overlooking the city on the front side of the hotel and then Lake Terrace Dining. It's a beautiful room, in the main area.

DR. CRAWFORD: Okay, I have no--

MALE VOICE: And the room is?

MALE VOICE: Lake Terrace Dining.

DR. CRAWFORD: Thank you. Perfect.

MALE VOICE: The Pompeiian is where we're having cocktails.

MALE VOICE: Okay.

DR. CRAWFORD: So everyone is invited to attend, spouses, pets, whatever you want to bring. We brought our pet to the last one. And spouses and guests are invited to attend. Tomorrow we start at 8:00 and we'll have a boxed lunch. A boxed lunch? We'll have a breakfast, a boxed breakfast available prior to the meeting right out here in the Mountain View Terrace.

MALE VOICE: The backside, the backside right out here.

DR. CRAWFORD: Okay.

MALE VOICE: It's a pretty area - - .

DR. CRAWFORD: And we, I know everybody has got flights and other things to get so we'll be done at 11:00 or 11:30 tomorrow. I hope everybody tries to come tonight. It's a lot of fun. We've got some comedy planned and a few other things.

One of the things I'm supposed to do is sort of give an overview of what happened yesterday, and a lot happened yesterday. We had really a great talk by Brian Moran on the future of focal therapy. Brian's done a lot of work, talked about the meetings in focal therapy, how it sort of started here a long time ago, probably 12 years ago. It really was Gary Onik who came here, discussed it. A number of us got interested and Brian has been doing a lot of it. Brian's done I don't know how many hundreds and hundreds of mapping biopsies and focal therapy. And the other thing, I think the culmination of it, there was a large meeting at the AUA with the FDA this year on focal therapy that was attended by several hundred people and that's the whole concept, that the FDA was looking at endpoints and it's not going to be survival rate, about how to prove that it's ineffective. So to me, and there's been a lot of different ways to ablate out there, to me that was a real positive step forward from that.

Chris Kane, who is not here, gave a great talk on robots

and all the new stuff and things that are happening, and ways to look at lymph nodes. We had a number of state-of-the-art presentations from industry that were excellent. Dan Petrylak moderated the next session and we talked to Dr. Finkelstein. We talked a little bit about his work in surgical oncology, radiation oncology, immunotherapy, measuring responses. Dr. Kim, who is not here today, an outstanding talk on cryotherapy. I think we all learned a lot from that. Tom Keane talked about ADT, and the importance I think of keeping testosterone less than 20. And there's a number of different agents that are capable of doing that and there are a number of agents that are not capable of doing that that we discussed, and we'll hear more about that today, in particular about some of the longer acting things such as Eligard.

Mitch Sokoloff gave a great talk on the future in high-risk prostate, kidney, and testes cancer. I guess these slides actually should be available to everybody if you want to look at them. Dan talked about the checkpoint inhibitors and then I gave a little bit of controversial talk on screening. So it was all well received.

I want to ask Dr. Schalken that question because this just came up in a conversation I was having a few minutes ago. We've been collecting PCA3s on everybody that walks in our clinic for probably seven or eight years, and we have several thousand. I have a group of men who've had radical prostatectomies, who have undetectable PSAs, and have a PCA3 signal. And I mentioned this to you before. How do you explain that? We want to write this up. What's going on there? Is it a harbinger of failure in the future? Sort of like an abnormal cytology? Or what do you think? Or is that just a fluke? Steve?

JACK A. SCHALKEN, PHD: So a sustained high PCA3 after radical prostatectomy.

DR. CRAWFORD: So somebody's had a radical prostatectomy, they come in, I do a rectal, I get urine, I do a PCA3, they have a PSA of less than 0.01 and they have a positive PCA3. I've already got 20 people like that.

DR. SCHALKEN: Yeah, so far still the only source that we have found for PCA3 is from the prostate and 60-fold higher in prostate cancer cells. So the only explanation could be

that there is still something left that drains to the urine. I mean we so far have not found any other source of PCA3. How long is the follow up that you have?

DR. CRAWFORD: So there has to be a PSA there too if we're going to, are you measuring PSA too with PCA3? That ratio?

MALE VOICE: It's urine PSA though.

DR. SCHALKEN: Yeah, but that's urine--

DR. CRAWFORD: Yeah, urine PSA.

DR. SCHALKEN: --PCA3 messenger RNA.

DR. CRAWFORD: Yeah.

DR. SCHALKEN: And the fact that you get a PCA3 score means that there is also PCA3 mRNA.

DR. CRAWFORD: Right.

DR. SCHALKEN: It's a good point that you ask that question because it's--

DR. CRAWFORD: Except I think didn't we ask, didn't was ask the group in Texas not to, just to report the PCA3, not the, didn't we ask them--

MALE VOICE: But if you get a number for PCA3 you have to have measurable PSA.

DR. CRAWFORD: Okay.

DR. SCHALKEN: So that would mean, I mean sometimes, and I seen more and more reports from colleagues from Scott's colleagues I mean that you get these shedding of the cells way through the collecting duct system. And if in one way or another they develop a mini clone of cells that's still active. But the only thing you would predict based on your observation that's at least in years thereafter you would get, I mean that it would increase.

DR. CRAWFORD: Yeah, Cowper's glands make PSA, Cowper's glands.

DR. SCHALKEN: Yeah but, yeah.

MALE VOICE: How many times are Cowper's left intact after a radical?

DR. CRAWFORD: Always. They're periurethral glands but they

have PSA. I mean--

MALE VOICE: It's in the UG diaphragm.

MALE VOICE: Well, except for the ones that are embedded in the prostate.

DR. CRAWFORD: They can give you PSA, - - they can give you PSA.

MALE VOICE: Messenger RNA, yeah.

MALE VOICE: - - so--

MALE VOICE: But they shouldn't have PSA3, I mean they shouldn't have that then. Right?

DR. SCHALKEN: How long--

MALE VOICE: That's just where the PCA3 comes from.

DR. CRAWFORD: I'm just saying to explain the PSA that may be, you know, you're seeing PSA expressing cells, they can come from those areas because we got that with RT-PCR a long time ago.

DR. SCHALKEN: Yeah, I think that's a good point but the PCA3 so far still is the most prostate cancer-specific transcript. So you would predict there is still something left. Whether that's a true bad prognostic sign you wouldn't know.

DR. CRAWFORD: Interesting. Well if anybody has any thoughts about that.

DR. SCHALKEN: I do know that - - .

DR. CRAWFORD: Pardon me?

DR. SCHALKEN: I do know that Frans also had a couple of them after radical prostatectomy, but he still had sustained PCA3 levels.

DR. CRAWFORD: You know what?

DR. SCHALKEN: Frans Debruyne, he also had similar cases, not that many.

DR. CRAWFORD: Oh okay. He did? He's doing his e-mails right now. He's not paying attention.

Anyway, what do you think of that Frans? See there.

DR. FRANS DEBRUYNE: Just seeing whether bicycling affects PSA.

DR. CRAWFORD: If what does?

DR. DEBRUYNE: Bicycling, bicycling?

DR. CRAWFORD: Bicycling, oh that doesn't.

DR. DEBRUYNE: Affect PSA.

DR. CRAWFORD: We studied that a long time ago. Ride the Rockies race. So also, we had some, Wim was telling me he can do 3D reconstructions now with a printer of our prostate, so I'm going to send him that.

Next to Wim is Karl Kreder who is new today. Karl is a professor and Department Executive Officer, Department of Urology at Iowa. Great guy, teacher, he does female/male urology, is involved in a lot of research, and actually spent some of his time in Colorado in his early years. So we welcome you Karl. And we don't have any new, other than Marty Miner is here. Right? You're new from yesterday. You were sort of here yesterday. You were here yesterday. Marty is, I didn't mention you, is a family practice doc is outstanding and he's from Brown and he's co-director of the Men's Health Center there, and has been intimately involved in a lot of this stuff with testosterone replacement and the articles and so forth and international societies and U.S. Society of Male Health, not Male Health but the Men's Health.

So anyway, we have, I encourage people to do questions even though we kind of screwed some people over yesterday by not answering a lot of the questions on the first day that all of a sudden appeared. I'm going to try to go through those today a little bit as we go. So with that I'm going to turn it over to Dr. Concepcion who is the moderator and Dr. Gomella is going to talk about hormonal therapy and then immunotherapy.

LEONARD G. GOMELLA, MD: I'm going to first?

RAOUL S. CONCEPCION, MD: Yeah, you go first.

DR. CRAWFORD: We've got to, everybody's got to stay on time today please. Thank you.

Featured Lecture: Hormonal Agents – Leonard G. Gomella, MD

DR. GOMELLA: Thank you Dave. Staying on time it's like speed dating, covering all of this in ten minutes but we'll try to do it here. So we're going to talk about hormonal therapy in the setting of castrate-resistant prostate cancer, and I use my New York-ese to talk too fast you can slow me down.

So here we are with all of the red arrows showing where have we impacted in prostate cancer over the years going back to Dr. Garnick's original work in 1984 and now extending it all the way through with the abiraterone and enzalutamide, which are the two agents we're going to spend most of our time talking about because those reflect the current state of affairs of hormone therapy for castrate-resistant prostate cancer.

One housekeeping thing to get out of the way is the fact that if you look at the NCCN guidelines anybody with castrate-resistant prostate cancer must maintain LHRH or LHRH agonist or antagonist or orchiectomy, hormonal ablation throughout the course of treatment. So that is the platform that all of this is built upon.

So a couple of years ago we redefined the entity known as castrate-resistant prostate cancer, which is officially defined as two consecutive rises in PSA while on androgen deprivation therapy with a testosterone of less than 50. We don't use the words "androgen resistant" or "androgen sensitive" anymore and we'll show you why in a couple of minutes.

We have some data that people with lower T tend to do better on androgen deprivation therapy, and we know that the LHRH agonists and antagonists do not get us down to the lowest levels possible that we see with some of the new medication.

So here's the initial treatment paradigm with metastatic prostate cancer. You initially get cell cycle arrest with death and apoptosis of the majority of the cells, but unfortunately for most patients with advanced disease somewhere around 12 months to three years later it tends to come back and we develop castration resistance. And how

does that happen? Because we now understand that we had activation of many factors that basically turn the androgen pathway back on.

So this is something Tom Keane touched on briefly yesterday, we know that patients, the lower the testosterone goes the better. This is controversial but again Tom showed this data yesterday that for LHRH analogs with advanced disease the lower the level the better patients tend to do, so clearly our goal should be to get the testosterone down low as possible. Traditionally when we're faced with castrate-resistant prostate cancer we have used secondary hormonal manipulation. But unfortunately these responses are rarely durable.

So what's the current state-of-the-art? The current state-of-the-art is that castrate-resistant prostate cancer maintains sensitivity to extremely low levels of androgens. How does it do this? We get androgen biosynthesis from adrenal precursors and de novo synthesis in the tumor cells themselves as survival mechanisms. Also, cells become hypersensitive to very, very small amounts of androgens through modifications in the androgen receptor, either increasing expression, mutations, or activation of androgen receptors. So getting the androgens to the lowest level possible is the goal with castrate-resistant prostate cancer.

This is just a snapshot of all of the different things that could potentially happen with adapting to the castrate environment, mutation, splice variance, intracrine tumor production, amplification. But the bottom line is it all explains why castrate-resistant prostate cancer comes upon us.

So the theories for castrate-resistant prostate cancer is that prostate cancer response to castration by synthesizing androgens from either weaker androgens or cholesterol precursors, the receptor may be up regulated or mutated in some way. So prostate cancer progression still occurs in low states of androgens or testosterone because it is still sensitive to these, to these androgens.

So where are we today? The newer castrate-resistant hormonal agents either act by androgen biosynthesis inhibition or androgen receptor pathway blockade.

Abiraterone and enzalutamide are the two FDA-approved medications that we're going to spend the majority of our time on. ARN-509 and the Tokai product Galeterone are also out there but we don't have a lot of data on them. The TAK-700, which was an androgen biosynthesis inhibitor has been terminated from its development because in the trial it did not prove to be superior, and probably suffered from the fact that secondary agents for CRPC were available. If this agent would have been around eight or ten years ago it probably would have been a blockbuster.

I am not going to talk about what we know already from the Cougar trial, the AFFIRM trial, the PREVAIL trial about the agents that are already approved. Those have been beaten to death. Since this is a forward-thinking group I'd rather talk about the information that's coming down the pipe that's either been presented at meetings the last couple of years and has not been officially published yet.

So to just talk a little bit about the agents, for those who are not completely familiar with it, abiraterone is a CYP 17 and a 17 lyase inhibitor. It ends up blocking the production of androgen and DHEA, and it does this anywhere in the body whether it's in the testicles, in the tumor itself, or in the adrenal glands. Abiraterone is extraordinary unique as an androgen biosynthesis inhibitor because it gets levels lower than we've ever seen before with any other drug that's been available.

This is the dosing, 1,000 mg with the official label being 5 mg of prednisone twice a day. Adverse effects, you have to monitor potassium, blood pressure, and liver function tests but it's generally very well tolerated.

Why do we need prednisone? The reason for this is because when we block the production of the 17-hydroxy pregnenolone to DHEA from the abiraterone you drive, you reduce the levels of cortisol which in turn increase ACTH, and unfortunately the precursors of the mineralocorticoids occur before the blockade of the abiraterone, so you end up getting increased mineralocorticoids by replacing cortisol. That can be taken care of.

Urologists are generally afraid of abiraterone in a lot of circles because of the steroid administration issue, but we've had a couple of publications out there including this

one that we presented at the AUA that basically says that you don't really get a lot of side effects with this very low dose of prednisone. Medical oncologists dish out 40/60/80 mg of prednisone. The 5 to 10 mg of prednisone a day for urologists should not be a concern.

Abiraterone clinical trials that are currently out there, we know about the Cougar 301 or 302. The IMAAGEN trial is ongoing and has some early data, and it's actually also being looked at in breast cancer right now. This is the IMAAGEN trial for M0, rapidly progressing prostate cancer. Basically there's outstanding PSA responses with 60% of the patients having a 90% reduction in their PSA with abiraterone. The last update that Chuck Ryan presented showed that it did extend in this M0 population. The median time to progression and the radiographic evidence of disease progression is still ongoing. So the IMAAGEN study is still being looked a prospectively, but up to this point you still haven't gotten radiographic evidence of progression.

Enzalutamide is MDV3100. It's an anti-androgen with no agonistic effects, such as bicalutamide. The agent targets the androgen receptor signaling. It also does, it interferes with multiple steps in transcription and translation. It has no impact on serum testosterone and does not require the co-administration of steroids.

Two current in process trials out there are the TERRAIN trial, which is primarily a European trial looking at enzalutamide versus bicalutamide in metastatic castrate-resistant prostate cancer patients, and again shows it's superior to bicalutamide monotherapy. In the United States at the AUA Dave Penson presented the STRIVE trial, which is essentially the United States' equivalent of the TERRAIN trial. Again, showing that particularly for patients with M1 disease it does improve progression-free survival. And for patients with M1 disease it does extend radiographic progression-free survival. For STRIDE we're waiting for more data on M0. It's not out there yet, but obviously this all shows that enzalutamide is better than bicalutamide as a monotherapy.

Enzalutamide is given 160 mg a day. It can be taken with or without food as opposed to abiraterone that you have to take without food or else you get too high of levels.

Adverse events with enzalutamide tend to revolve around fatigue and dizziness. Lately there's been increasing attention on falls and related symptoms, muscle weakness potentially with enzalutamide, so something that's getting a little bit more attention.

There's a whole bunch of ongoing enzalutamide clinical trials that have all sorts of different names associated with them, the PLATO trial, the PROSPER trial, the UPWARD trial, and again I refer you all to the slides for this. EMBARK is an interesting three-arm trial with enzalutamide, enzalutamide and leuprolide, and leuprolide alone for patients with non-metastatic prostate cancer, and again who have rapidly progressing PSA, and that's currently enrolling patients.

When you compare enzalutamide and abiraterone one is a CYP 17 inhibitor, one's an anti-androgen. Unique side effects you can see are summarized here, abiraterone on the label requires the administration of prednisone, but that's not always done in a lot of centers, and there is some suggestion that abiraterone, at least in our market, is a little bit cheaper than enzalutamide.

To touch briefly on some new things going on. ARN-509 is also an androgen receptor blocker that's been picked up by Janssen. It's a competitive inhibitor. It is seven to ten times more active than bicalutamide. So Janssen is now in the area of the androgen receptor blockade. They have a series of clinical trials. The big one is the SPARTAN trial for non-metastatic castrate-resistant prostate cancer. But they also have trials in M1 disease.

This is the future, molecular profiling. This was the really pioneering work from Dr. Antonarakis at Johns Hopkins who looked at CTCs and was able to show that basically if you have this mutant in the androgen receptor enzalutamide or abiraterone tend not to work that well. These will be combined. This is a big, a big trial by Alliance which is a new, one of the new groups that's out there that's going to be looking at abiraterone and enzalutamide, and we're anticipating results in this particular trial of enzalutamide versus the combination about four or five years from now.

And this will be consuming us for years, sequencing

overlapping, layering, whatever, whatever Dr. Crawford decides that we're going to be calling this.

All of these things will have to be combined in one way or another to figure out which is the best way to go with things. So the bottom line is prostate cancer patients have good reason to hope. A lot of good things going on. These drugs are orally administered, which makes is a lot more convenient for the patient than coming in for confusion, for infusion.

And lastly David, I have something to show you here. I found out, I know you love Philadelphia.

DR. CRAWFORD: Filthadelphia.

DR. GOMELLA: Do you realize that this hotel was founded by Mr. Penrose, a Philadelphian?

DR. CRAWFORD: No.

DR. GOMELLA: Yes. Mr. Penrose is from Philadelphia. And also, walking down the hallway--

DR. CRAWFORD: A lot of people try to get out of Philadelphia. I can see why.

DR. GOMELLA: That's true. That's true. They bring our culture to you here in Colorado.

DR. CRAWFORD: And we straighten them out, okay.

DR. GOMELLA: And lastly, I was walking down the wall of pictures and actually stumbled across somebody who I've actually had the finger in their rectum, but I'll leave it up to you to decide who it is. Thank you.

MALE VOICE: Caitlyn Jenner.

DR. GOMELLA: No it was not Caitlyn.

[Applause]

DR. CRAWFORD: So we have, I guess we actually do have a couple of minutes for questions. So STRIVE and TERRAIN trials are phase II trials. Correct? How can you say that enzalutamide is better than Casodex based on a phase II trial, a randomized phase II trial?

When you do randomized phase II trials you really, they're

not powered for that. You're not supposed to compare things, and every pharma company does that, and every person does that. They compare the two arms in a randomized phase. That is heresy. I mean it's statistical heresy in my opinion.

RAOUL S. CONCEPCION, MD: I can actually help you out on that because I was one of the PIs on STRIVE with Penson and Armstrong because STRIVE was a combined, you could be M0 or M1. And the comparator arm was bicalutamide. What was exclusionary in STRIVE if you had been on bicalutamide and you had had PSA progression while on bicalutamide you were excluded from the trial.

DR. CRAWFORD: No but the point, the point is it's a phase II, it's a randomized phase II trial and you're not, am I wrong?

DR. CONCEPCION: No right, right but I mean I don't think these were intended to be registration trials.

MALE VOICE: Right.

DR. GOMELLA: I mean phase III is a registration trial. I hate to say I think that everybody is just trying to show that bicalutamide is yesterday's news and they have some data to show that bicalutamide is secondary hormonal manipulation, doesn't work as well as our new abiraterone and our enzalutamide from a very narrow perspective. They're not registration trials but they do show that these monotherapies, enzalutamide and abiraterone, are superior and probably should be knocking off secondary hormonal manipulation that we all do with bicalutamide, and I kind of think that's what they're pointing towards.

DR. CRAWFORD: The point is it's not powered to do that. You know, it's a randomized, it's, it's two phase II trials that people put together and I hear it all the time. Well we want a comparator to kind of see what it is. But you can't, no, we're not going to compare it if you read the statistical part of it it says that. Mark Garnick, am I not correct? Huh?

MARC B. GARNICK, MD: Totally correct.

DR. CRAWFORD: It's very, it's very seldom that he agrees with me.

MALE VOICE: You're always right.

DR. GARNICK: I do have one thing. You know we have never used the b.i.d. prednisone with abiraterone. You can get away perfectly fine with just 5 mg. So if the urologists are using this there's no reason to--

DR. GOMELLA: And that was, I mean and that was one of the subtle differences between the label and STRIVE was the 5 mg a day of the prednisone.

DR. CONCEPCION: Well that was IMAAGEN. Yeah IMAAGEN.

DR. CRAWFORD: Even IMAAGEN.

DR. CONCEPCION: IMAAGEN was 5 mg daily.

DR. GOMELLA: I'm sorry, IMAAGEN, excuse me.

DR. CRAWFORD: IMAAGEN.

DR. CONCEPCION: IMAAGEN.

DR. GOMELLA: IMAAGEN. I'm sorry.

DR. CRAWFORD: And some people don't even use it but I think 5 mg is probably reasonable. No, that was a great presentation. I just get perturbed when people do randomized phase II trials and they start doing a comparison. You see it at ASCO. You see it everywhere they do it, and it's not legitimate.

DR. CONCEPCION: But do you think it's legitimate to have on NCCN, do you think it's still legitimate to have bicalutamide as an option in patients without visceral disease in castration-resistant prostate cancer? I mean that doesn't make any sense to me either. I mean but it's in the guidelines.

DR. GOMELLA: They're in there. The AUA has them too.

DR. CONCEPCION: Yeah.

DR. CRAWFORD: Some people respond.

MALE VOICE: How often are patients getting endorectal MRIs in the, to make sure that they don't have an anastomotic recurrence before you consider them M1 as opposed to, before you consider them M0? Has that been a requirement in the IMPACT study?

DR. GOMELLA: Endorectal MRIs?

MALE VOICE: Yeah. I mean one of the, I mean there have been a whole series of discussions by the FDA and actually convened a panel on the development of drugs for non-metastatic castrate-resistant prostate cancer, which is basically a rising PSA after definitive local therapy, and one of the points that came out of that was the need to rule out anastomotic recurrences in those patients following prostatectomy.

DR. GOMELLA: The best way to do that is with a color Doppler and a biopsy. You don't need an MRI actually. If you wanted, the best data out there on anastomotic recurrence is using a color Doppler. If you have a signal there and you do a biopsy it's positive about 80% of the time. But the multi, Marc is very pencentric and they love the endorectal coil MRI but the multi, we don't do any, at our place don't do any endorectal. It's all multiparametric, you know, 1.5 and 3T MRIs. We don't use the endorectal coils.

MALE VOICE: But has that been a requirement in any of the eligibility criteria in the studies that you were discussing.

DR. CONCEPCION: Not that I've seen. I mean it wasn't for STRIVE, it wasn't for IMAAGEN.

DR. GOMELLA: But David, you did work on, you did work on the screening group for IMAAGEN. Didn't you? For people and one third of patients had occult disease unrecognized.

DR. CRAWFORD: What about it?

DR. GOMELLA: Didn't you do, didn't you, for a minute could you tell us about that experience.

DR. CRAWFORD: Yeah, it actually won best poster, one of the best posters at the AUA this year. We basically, and it's not, it really isn't that new because it was looked at with some of the other trials, but they looked at people that you thought were not metastatic when you did a scan on them and that 38% of the people, is that right Tracy? Was it 38%?

TRACY MCGOWAN, MD: 37.

DR. CRAWFORD: Sorry. Ended up, ended up having metastatic disease when we didn't think they did. What else was new in IMAAGEN that we didn't discuss?

MALE VOICE: Based on what? Based on a bone scan or based on a CT or what?

DR. CRAWFORD: Both.

DR. CONCEPCION: Both.

DR. CRAWFORD: And we have, and it wasn't sodium fluoride PET either, just technetium scans. Was there anything else new in IMAAGEN that we need to know about? Tracy?

DR. MCGOWAN: No, still have median PFS which is good for patients and we'll update again this year and see - - a lot of patients have gone for a really long time now.

DR. CRAWFORD: And in light of what was said yesterday about FDA approvals on delaying mets and progression that should be pretty strong. But that is a phase II trial, it's not a phase III trial. And 5 mg, okay? Excellent. Any other questions? I don't see any, anybody, if anybody wants to shoot any questions up. Did anybody actually put a question in just now in the last 15 minutes? Because I don't have any. I just want to make sure we don't have another problem like we had the other day.

Okay.

Featured Lecture: Immunotherapy – Raoul S. Concepcion, MD

DR. CONCEPCION: All right, well first of all I'm Raoul Concepcion. I want to thank, first of all I definitely want to thank the guys in the back. So about an hour ago I was trying to rearrange slides and things were going well and then 30 minutes ago all of my slides had X's on them. So I sprinted down here in my jeans and thankfully the guys in the back were able to rescue my slides so I actually have a talk to give. Otherwise, I'd be experiencing the wrath of Crawford I'm sure. But I do want to thank David for inviting me as usual. This is, I haven't been here as long as many folks but I have enjoyed coming here. but it's also, it's also a curse because sometimes, I don't

know if any of you watch the Food Network but sometimes, every time I get this invitation to come talk at Crawford's meeting I always, it's kind of like if you watch the Food Network and *Chopped* these chefs they're opening up these baskets to see what they have to cook with. So I always open up Crawford's agenda saying okay what is he going to have me present this year? Because I have no idea. So Keane and I were talking about this. So now I get this thing well you're going to talk about the role of immunotherapy and the advantage in advanced prostate cancer. So it's a little intimidating, especially with Petrylak and Finkelstein, you know, Mr. Immunotherapy themselves. So I'm going to sort of do the best that I can and kind of muddle through this.

So this is for all of Michigan friends, specifically Finkelstein. So they are pre-season number one again so just FYI. Okay?

So I didn't really know how to structure this talk so I thought I would come at it as sort of where we've been, and much of this has already been reviewed, some of it just now by Lenny, but a lot of it has been reviewed by Dan and certainly Tom Keane yesterday. So this is kind of where we started with the treatment of advanced prostate cancer. This is sort of the seminal paper by Huggins and Hodges looking at the effects of castration on advanced prostate cancer in rats.

And I stole this slide from David actually. So this is sort of the mechanisms and ways that we can induce castration levels of testosterone. Obviously there's orchiectomy, then there was the development of LHRH analogs. Many, many years ago obviously we used DES. You still get some extra gonadal production from the adrenal glands and so we've got all these new androgen access blockades. So we've come a long way in terms of being able to really get to very low levels of castration.

So this is very, this is a slide that Lenny just showed. This is the chronology of FDA approval drugs. We know that prior to 2010 all we had was docetaxel. But since that time we've had a plethora of new drugs approved. This is the same slide that Lenny showed. I'm not going to go over this but again, we have had as we move, as we've been moving forward we have had a multiplicity of drugs all with

a survival benefit, which again has really made it very exciting times for us in this space of metastatic castration-resistant prostate cancer.

So given that this is the future of urology, the future of therapy, where are we going next? So if anybody wants a copy of this article, this was a very nice review article written by a Arul Chinnaiyan up in Michigan, and it's basically advancing precision medicine for prostate cancer using genomic testing.

MALE VOICE: What institution was that?

DR. CONCEPCION: It's Michigan. Yeah. So in this article basically this is a pathway which I think we all need to sort of recognize, and as you look at this pathway we're already addressing some of them. So we've got androgen access inhibitors, and AR antagonists, but again we've got all of these drivers, and again I think we have to be very, very cognizant. This is the way we're going as we start looking at panomics, whether it be genomics, transcriptomics, or proteomics, or as they're doing up at U of M even metabolomics. Ganesh Palapattu, who is the head of Urologic Oncology, gave actually a very nice talk at the AUA looking at their work on metabolomics.

These are some drivers that they've already identified and these are some of the inhibitors, and again I think Karen at Lenny's institution is very big into DNA repair molecules. And again, a lot of this is going to go towards basically this targeted therapy.

This is a slide from Antonarakis and Andy Armstrong. These are all the biologic mechanisms that are driving CRPC. So we not only have AR-dependent mechanisms but we also have AR-independent mechanisms. And like Lenny said one of them that everybody is looking at right now is the AR-V7 spliced variant that Antonarakis reported on last year. And we know that there's a drug that has just been finished their phase II trials and Mary-Ellen Taplin presented, which is Galeterone, and Galeterone has a little bit of enza, it has a little bit of abi, but it also has a third component where it actually can knock out the rest of the AR.

So this is a slide that kind of is a summary of where we've been. So we've got some hormonal therapy, we've got targeted therapy, we've got traditional cytotoxic therapy.

We do have bone targeting therapy including radium-223, and as you know we also have immunotherapy. And this was slide talking about immunotherapy in its breakthrough year in 2013. So we know that there is one immunotherapy that's approved right now and it's an active immunotherapy, and that's sipuleucel-T.

But if you look at the progression of immunotherapy it all started back in the 1890s. There was a surgeon named Coley. He actually took, he actually injected a mixture of Strep pyogenes and Serratia into tumors themselves to try to stimulate an immune response. And then again you have this whole development of everybody looking at immunotherapy. And I'm not going to bore you with this.

So the immune system, so you not only have innate but you have adaptive, and so these are your basic characteristics. The innate system is really non-specific. You don't need antigens, but there's also no memory. It includes macrophages, dendritic cells, natural killer cells, as well as neutrophils. In the adaptive it's more specific, it's very specific, it's antigen generated, it's antigen stimulated, and obviously what's beauty about it is that you do have memory and it's basically T call and B cell mediated.

These are your basic cells on the innate side. You've got neutrophils, dendritic cells which are, you know, macrophages, and NK cells which we're going to talk a little bit about. The tumor environment, and again I'm going to run through this pretty quickly, again it's this constant interplay between your innate adaptive as well as the tumor itself. So this tends to happen. Is that you get antigens that are released, they get presented by the antigen-presenting cells. This all happens pretty much in the lymph node tissue, and then it gets into the peripheral tissue and you get replication and then you get basically specialization of your T cells.

And these are your general approaches for cancer immunotherapy. You have active immunotherapy, and like Steve was talking about yesterday you also get adoptive cell transfer. And again, so on the left-hand side you see the basic mechanisms of vaccine. So on the top part you have what we all know as sipuleucel-T, which was approved in April of 2010 for metastatic CRPC. For those of us who

have used it it's basically three infusions two weeks apart. You do have to have apheresis. The cells get sent to the Valeant/Dendreon plant and then they're re-infused. We also know that, like we talked about the other day there's also another vaccine called Prostvac, and they completed their trial which was PROSPECT and as we talked about that's going to be probably reported in the next couple of years.

Also, what we know is that, and Dan gave a nice talk on the use of checkpoint inhibitors in bladder cancer. They've done a little bit of that in prostate cancer. Chuck Drake as you know has done some work with that specifically looking at an anti-CTLA4. And again, we know that these checkpoint inhibitors whether they be CTLA4, PD-1, PD-L1s actually put the break on the immune side.

So again, this is sort of a schematic, looking at the rationale of the use of checkpoint inhibitors. So again, it's another area where people are especially in bladder where Dan is doing a tremendous amount of work using anti-PD-1s and anti-PD-L1s. And the whole goal here as Chuck has told me is that what we're trying to do with these checkpoint inhibitors is take off the brake and let the immune side just go nuts. And again, that's another schematic looking at the same thing.

I'm going to, I'm going to fly through this. So here's where we stand now, and again I'm going to kind of wrap up here. So here's where we stand. This is basically the top ten biotech companies in the world in terms of revenue, in terms of billions of dollars. So you've got J&J, Novartis, you can read the list. But this is no longer, this is not just the big boys. So over the past few years you've had a significant amount of money being infused into startups. You had Kite that went public in June of 2014. Their market cap was 2.2 billion, and then you had that should be Juno in December of 2014 at 2.4 billion, and then two weeks ago you had a company out in L.A. called NantKwest that's market cap was 2.6 billion. So all of these have gone public over the last year. And again, these companies are very, very early. Their products are still in development. So in 2014 there was close to five billion dollars raised just for these small companies.

So I'm going to spend a little bit of time, because I've

got 18 seconds, looking at this, looking at this company called NantKwest. The company was actually called Conkwest, and what they found, who read the book *The Immortal Life of Henrietta Lacks*? Great book and basically it's about the HeLa cell line, and the HeLa cell line were cells grown in culture back in the 50s. Henrietta Lacks was an African-American woman who had invasive cervical carcinoma. Howard Jones was the gyn-onc back then in the 50s who actually did a biopsy. And her cell line actually grew in culture and has basically been the cell line which has been used for all types of genomic testing. So it's called the HeLa cell line because it's the first two initials of her first name and last name. So it was Henrietta Lacks. So if you want to read an interesting book about, it actually is about ethics as well. It's called *The Immortal Life of Henrietta Lacks*.

And so basically what, we're having a breakthrough now in these therapeutic modalities. We know about monoclonal antibodies, it's basically antibody-directed cell kill. You also have this innate side called natural killer cells, NK cells. And then now also you have the introduction of CAR-T cells, chimeric antigen receptor therapy. And so building a CAR-T cell has really been a hot item. This is what Juno does. This is what Kite does. And again, I'm going to kind of rifle through this. There are some drawbacks from CAR-T cells which include tissue, you know, cell expansion as well as some of the side effects that you can get with the infusion of CAR-T cells.

NK cells the reason why I mentioned this concept about Henrietta Lacks is that a company out of British Columbia, a guy named Hans Klingemann actually identified a natural killer cell that did not have, that did not have what they call killer immunoglobulin-like receptors. So it was completely non-suppressible by the tumor cell. So this was, you know, this is sort of an off-the-shelf if you will NK cell. And he was able to grow this in culture. And so now what they're doing, what this company is doing they're actually being able to activate these NK cells, retro infecting them with monoclonal antibodies, and as long as you can basically identify the isotope, the antigen on the tumor cell, you can actually infuse these. There are also, they also know that you can, that these have high affinity C16 receptors and these C16 receptors bind to the backside

of the monoclonal antibody. So what you can do with some of these, with these NK cells, if they have this high affinity C16 you can actually again infect the, transfect these cells and now you have these high affinity natural killer cells, and then what you can do is you can then deliver these with a monoclonal antibody therapy like Herceptin. And so now only do you have the monoclonal antibody like Herceptin or trastuzumab but you can also now deliver these activated natural killer cells. You can also then obviously just transfect them with the antibody itself. So now you have a tumor-activated natural killer cell, and again you can infuse these directly.

So that's a very quick overview. That's sort of a, you know, this is kind of where immunotherapy is going. You know, Steve made a comment well there's not a whole lot going on right now in prostate. Obviously Dan's doing some great stuff in bladder, but again this is kind where the world is going. We're going towards a more targeted-based therapy, stimulating the immune system, and much of this is going to be completely predicated on panomic testing. [Applause]

Discussion

DR. CRAWFORD: Well that was very good. Stay up here.

MALE VOICE: Except for the Michigan part.

DR. CRAWFORD: No, I didn't know you knew all that because I didn't know half of that.

DR. CONCEPCION: Well, it's like Fernando said, he goes Raoul, no matter what you present people aren't going to know about it anyway.

DR. CRAWFORD: Yeah, especially when you read books like that you know?

DR. CONCEPCION: Yeah.

PHILIP GINSBURG, MD: Raoul, I think I can comment on a few things that you mentioned. I actually have a background in microbiology and immunology and when you think about it when you're using the BCG for what 30 years? You know, in the kidney and the bladder. In countries like South Africa we were vaccinating kids at birth with BCG and obviously

for TB. So I kind of see this coming around as a full circle, that we've gone from not quite sure what to do with these potential therapies, where to base, you know, attack the pathways. And part of the rampant unraveling of these things has been our elucidation of the biological pathways, the development of molecular profiling, being able to bring biomarkers into place so that we can target which points in the pathway we should be looking at to develop drugs that can inhibit or stimulate depending on the situation.

So I think it's very exciting. I think this is the next wave in terms of therapy. But at the same time I also think that what everyone is starting to recognize whether they're clinicians or laboratorians and so on is that we need all of the tools. It isn't due to one single modality approach to any given cancer, and the cancer is our common enemy. So I'm pretty excited to see that there is sometimes gradual, maybe sometimes fast adoption of new and innovative diagnostic methods, genetic analyses, a better understanding of the pathways. And also most all of the big drug companies and the smaller biopharmas are all looking at this as their wave for the future in terms of new drug development or adding additional indications for their therapy. I actually think you've touched on one of the most exciting modalities and adding a very powerful extra tool in our attack on cancer. Thank you.

DR. CONCEPCION: Yeah I think that, I mean I think as we understand these as a patient of mine and friend says as we understand these cloaking mechanisms that these tumor cells have to be able to overcome these, you know, overcome these mechanisms is going to be really important. I mean Dan do you have any comments? I mean you're doing a heck of a lot of work on PD-1s and PD-L1s.

DANIEL P. PETRYLAK: So I think that the premature barrier of the checkpoint inhibitors has been over exaggerated and I think we'll see something in the next year or so. It may not be the same level of activity that we see with bladder cancer but there's something and it needs to be teased out.

I think one of our meetings this week where talked about sequencing we often forget that chemotherapy interventions have an effect on the immune system. There is a removal of T-reg by giving docetaxel. We've seen that in breast cancer specimens. So I think that as we understand more

about how these drugs interact together. You gave a great talk on the back pathways that may be involved with immune treatment and really one treatment affects the other.

DR. CRAWFORD: Right.

DR. PETRYLAK: And it's going to be very, very important that we look at the basic science of how we integrate that in taking care of our patients.

DR. GINSBURG: And could I add one more comment to that what you just said? But when I went to talk to insurance companies about certain tests, genetic tests, - - EGFRs, KRAS, and that sort of thing. The initial feedback was we'll pay for one. Right? And I'd say well why? This is not a hereditary thing that now you're doing a - - . What we're forgetting is that the drugs that you're talking about induce resistance over time. And I think there's the reason to continue with the monitoring and the best tools that we have available right now are molecular based and epigenetic type testing so that we can continue to monitor that evolution. And I think that enables us to change because we can either take out that therapy and allow the cells to return to normality or look at alternative therapies.

DR. PETRYLAK: I think that's a terrific point because we assume, I think that there's too much of an assumption that these are static systems, they are plastic, they change. And a perfect example of that is the experience we had with PD ligand. So there is data that suggest that chemotherapy will up regulate its expression, and perhaps the reason why we have a discrepancy in those patients who respond and those who don't is that the tissues that we assayed, some of which were at the time a cystectomy, may not have been the right things to look at. So I think that's a superb point. We need biopsy/imaging systems to really tell us what's going on.

STEVEN E. FINKELSTEIN, MD: So going along with talking about checkpoints. Right? So it comes back to why does PD-1 kill cancer? Does PD-1 or those drugs actually kill cancer? No. All it does it takes the brakes off second signal, breaks tolerance. So in order for you to generate immune response you need a couple of things. Right? You need a T cell usually, there's reactive against a target.

You need a target to be shown. Right? And then you need that break usually for second signal.

So one thing that Raoul talked about that I'm worried about, which is so we tried an approach similar to CARS [phonetic] and NCI which is the approach that we're going to build the right T cell to go after cancer. And what we found was humans are not very good at figuring out what the actual T cell is going to be that's going to wipe out cancer. Look at Antoni Ribas' data for melanoma. What's the actual thing that we're going after when PD-1 works? It's a whole bunch of things. So trying to pick if you're a large pharma company and say I'm going to built this and this is going to be for everybody is very difficult. A more likely solution is to build a local therapy, whether it be radiation, cryotherapy, brachytherapy, HIFU, that can actually stimulate molecules to be up regulated in what would be non-self ways that can be augmented with immunotherapy.

And so I would encourage as urologists, as one who is a surgeon, right? What work is currently being done to combine cryo and look at with immunotherapy. HIFU with immunotherapy, there are opportunities there of which my urology brethren can definitely explore.

DR. CRAWFORD: So Raoul you sort of expressed disappointment that not much is going on in other things like prostate. We've sort been blessed to have the first immunotherapy in prostate.

DR. CONCEPCION: Right.

DR. CRAWFORD: Which is sipuleucel-T. And as we study it more, I mean sipuleucel-T is innocuous from the standpoint of side effects compared to some of these other things we're doing, a little bit of fever and chills and things like that. You know there's this worry about cardiac and CNS an whatever. I think that's sort of gone by the wayside, but and as we know as you use, move these things up earlier, and we showed that slide about when you got a PSA of less than 22 and use it, it seems to be a hell of a lot better and it's not lead time biased and weighting, and I think we see that with a lot of them. So and yet I find that people don't embrace it, and particularly medical oncologists. I mean, you know, it's quite variable. And I think the

interest with sipuleuecel-T is that in large practice groups it's been significant, among certain urologists it has but it's just not, it's not caught on the way it really should in my opinion.

DR. CONCEPCION: I mean as you know David the problem that we are facing with urology is this whole educational barrier in terms of lack of identification and the understanding of the environment of castration-resistant prostate cancer. We've just not done a very good job historically in identifying these patients. And you, myself, Neal, and a number of us have been trying to drive that point home. We obviously published the RADAR paper. And so I think again going back on a more global view about the role of urologists I am a firm believer like Dan Petrylak said in the Journal of Urology this is not a, you know, castration-resistant prostate cancer needs to be managed in a multidisciplinary approach, you have to have a physician champion whether it's a urologist or oncologist but I think it's incumbent upon the urology world to identify these patients because of the quartile data, to identify these patients early, treat them early. I mean I think you and I both agree that's kind of the key and we've just not done a very good job of doing that.

DR. CRAWFORD: Yeah, and the other thing, the other thing was when sip-T came out it was just sort of dangling by itself with this 90,000 dollar price tag that everybody just sort of criticized. You know? You see that but yet we'll pay 80,000 dollars for IMRT or we'll buy a three-million-dollar robot, or we'll do this, or we'll do that. The urologist didn't have that sort of well I get excited about several months survival benefit. Now that we have other agents out there that are just as expensive that's not what I hear anymore. I'm just, and the education among urologists but also of medical oncologists. I mean they don't seem to be picking up on it. They don't do, now that we got CHARTA data, which has nothing to do with what we're talking about right now, and everybody is talking about that. Dan, what do you think?

DR. PETRYLAK: Now again I think, I agree that we need an educational effort, medical oncology, urology, all across the board. Why did sipuleucel-T not pick up? Well I think that again there was a lot of secondary data that was not presented that's coming out now that's really making the

case very, very well. But again, I think the whole issue is education and making sure people understand when somebody truly is progressing, when they should be taken off therapy, when they shouldn't be taken off therapy. It's not, not that easy.

DR. CRAWFORD: We've heard all the things why the PSA doesn't go down. You know we heard that and we heard well this and that, well you can't give it with steroids, well you can't give it with abiraterone, well it's like--all these questions got answered.

DR. PETRYLAK: Yeah.

DR. GOMELLA: But they're not being drilled in.

MALE VOICE: Right.

DR. CONCEPCION: And again I think the problem is in the urology world is that we tend to look at hormone-naïve, localized prostate cancer, the monitoring mechanisms that we use we then move them over into the castration-resistant prostate cancer patient. And they're obviously two different disease states but we treat them the same. We have historically used the same monitoring scheme vis-à-vis PSA only, and it's really quite simple. The minute we give them hormone, the minute we deprive the cells, deprive the patient of hormones we get less PSA production by the cells. And so we still say oh PSA of 10 must be okay. Well, PSA in a guy of 10 who is on hormones is markedly different in terms of tumor volume than somebody who's hormone naïve. But that's the problem that we've had in urology.

DR. PETRYLAK: So the other problem too in the waiting room when you see patients are comparing their PSAs in totally different clinical states--

DR. CRAWFORD: Right.

DR. PETRYLAK: I've actually seen people get terribly upset when their PSAs have been 10.0 and their counterparts have been 0.4. Again, I think that we live and die by PSA but we over interpret it.

DR. FINKELSTEIN: So two points, one a comment. So yesterday I talked about the trial we're doing. So with respect to, you know there doesn't, didn't Dendreon's Provenge doesn't

drop your PSA. Well, now we can finally take pictures before and after what we're doing. I had a patient who was one of the first patients on the trial come back in his six-month assessment. We radiated his spine and he had pelvic mets at the same time. Right? So we radiated his back. We did not touch his pelvis. Immediately after radiating he had metabolic changes in where we radiated but not in his pelvis. Finishing Provenge now six months out his pelvic disease is gone. I didn't touch his pelvis. He's not on hormonal therapy because he doesn't want to be on it. Not everybody who gets Provenge is on androgen deprivation. You have to be on androgen deprivation to get the second-generation hormonals, but not everybody who gets Provenge wants to be on androgen deprivation. So if that data came out 2010, if you could see the disease go away people would believe Provenge a lot more.

The other part I'll mention is there is nuances to the quartile data. The quartile data was data that when broken down suggested that in the lowest burden of disease patients did better. However, for every quartile Provenge worked.

DR. CRAWFORD: Right.

DR. FINKELSTEIN: For every quartile. Right? So when you think about this we say we've got to give it early and that's because the quartile data suggested it worked early. But that didn't mean we were supposed to throw the baby out with the bathwater, that you couldn't pull the trigger on immunotherapy at any time point in the burden of disease. Indeed, in Rosenberg's data initially your burden of disease was not a remarkable point whether you responded to IL-2. Is your burden of disease remarkable if you respond to checkpoint inhibitors?

MALE VOICE: It depends.

DR. FINKELSTEIN: It depends. The whole point is that immunotherapy is an animal that we do not completely understand, and now is a good time for urologists to get in the game.

DR. CONCEPCION: Yeah, I mean I think those of us that lived through the Provenge rollout I think it is probably an MBA case discussion point on how not to roll out a drug. I mean they completely, they completely muffed the rollout of

that and didn't recognize where the patients were being harbored or the patients were being followed. Didn't have any idea, like many of the companies in here. Listen, this is a space where they've never talked to urologists. I mean we're different animals and it doesn't matter the company. But at the same time an MBA case study on how to really effectively message was actually done by Amgen when they tried to roll out Dmab. They had never had, they had never had exposure in the urology world and they spent a good year and a half consulting with urologists how to get that messaging out. Bayer has done a similar thing. And I think all of the companies are recognizing that.

So I think we're all saying the same thing. This is a huge educational hurdle and I think David's point was well taken, is that Provenge got a big hit because I think it wasn't, yeah it was the 90,000 but it was also the concentration given the fact that it was only three cycles. And they looked at it as 31,000 dollars per cycle, which was a huge hit. Well ipi came out six months before and nobody was really talking about the 125,000 dollars it cost to be on ipi.

DR. PETRYLAK: The big difference between ipi and Provenge again lies with the clinical trial design and the competence of those people who did it before. But the fact was is that the Dendreon data stopped following patients at three years.

DR. CRAWFORD: Right.

DR. PETRYLAK: You cannot see if there's a tail which is what we see with ipi, which is what we see with some of the other immunotherapeutic agents. Probably what we would have seen with Prostvac as well had the trial continued on. But that trial needed to be followed for a longer period of time and I think that the other complication - - following.

DR. CONCEPCION: Yeah, so I think what is good is that what Dendreon did is that they did the PROCEED registry which is ongoing and we're analyzing that data constantly, and it was basically, what was it Jim? 2,000 patients that we're following and Matt Cooperberg is, I mean it's very much going to be, what you're going to see out of that is multiple abstracts, very much like what UCSF did with TAP in CAPTURE. So we're looking at the first 2,000 patients,

or not the first 2,000 but I think we started accruing PROCEED in about late 2011/early 2012. We've got 2,000 patients in and we're constantly churning that data and there's lots of abstracts coming with that. And again, I think that will be a very nice registry data trial that hopefully will get a lot of good data from in terms of follow up and how patients do, especially as they change over therapies. James? James has a question back there. Your favorite fellow.

JAMES LUGG, MD: [Off mic] - - and is metastatic disease always found in the primary?

DR. CONCEPCION: Of course not.

DR. LUGG: - - do they start - - ?

DR. CONCEPCION: I mean, so the question was are the clones that are found in metastatic disease in prostate always found in the primary? You know, the problem is we don't do enough biopsies of the metastatic lesion to know. And Jack you can probably--

DR. SCHALKEN: Well Raoul, I think there is really a lot of data on that at the very moment from I think roughly 14,000 cancers being - - . And I think the picture that emerges is that usually one clone from the primary metastasizes. This does not mean that all of the metastases are homogeneous. I mean you will find again subclonal variation and it's one of the points that I would like to bring to all of the immunotherapists we have to realize that at the time that you're using the therapy at the moment you are fighting a dragon with nine heads, and each head behaves in its own way and has its own resistance mechanism. So probably what we're trying to do is simply not possible at that point of the disease. I mean you have lost the race, and maybe, maybe immunotherapy is the most hampered by that fact that you're attacking multiple clones with multiple resistance mechanisms. So the best--

MALE VOICE: Can let me come back on that one.

DR. SCHALKEN: Yes, later on.

MALE VOICE: Yeah.

DR. SCHALKEN: I mean I think the best thing you could do in immunotherapy design your trials in patients much earlier

in the disease process. I mean BCG does not work on the very aggressive disease, a relatively mild progressing disease. So I think that's the biggest challenge that we have; subclonal heterogeneity, the different mutations, multiple resistance mechanisms. I mean we could talk about immunotherapy probably another two or three days but you have to realize that one of the most powerful things cancer cells do is to secrete high levels locally of immunosuppressive cytokines. So I mean it's a tough cookie that you're fighting here.

MALE VOICE: Dan, aren't they doing a trial in high-risk patients, non-muscle invasive, using BCG and an anti-PD-L1? Isn't Roche or Genentech doing that trial?

DR. PETRYLAK: It's just going to be a straight PD-L1.

MALE VOICE: Okay.

DR. PETRYLAK: No combo.

DR. SCHALKEN: Great.

DR. PETRYLAK: It's going to open very shortly.

DR. CRAWFORD: So I think we have some - - . You had a list of the people - - ?

DR. GOMELLA: Yeah, we're moving along. So I think from an industry--

J. CLIFTON VESTAL, MD: Raoul, one more, one more--

DR. GOMELLA: Go ahead Cliff.

DR. VESTAL: Just a statement. Sorry to interrupt you. Not really.

DR. GOMELLA: Of course you're not. Shocking.

DR. VESTAL: But the question is meant to be what Eric said earlier, which is this is an opportunity for urologists to get in on the ground floor with therapy of the primary disease. Something probably should be done as opposed to in the past where we did nothing with a primary tumor in prostate cancer, a multimodal approach is certainly probably going to get us more mileage. That includes immunotherapy, chemotherapy, and hormonal therapy, the whole kit and kaboodle with all of the different models we

have. So I would think that any study going forward should probably have some arm that has treatment of the primary as a necessary event.

State-of-the-Art 10-minute Presentations from Industry

DR. CONCEPCION: Point well taken Cliff, James, excuse me. All right, so let's go ahead and try to stay ahead of schedule and we're going to have a series of presentations from our pharma partners, and the first one will be from golfer extraordinaire Stuart Atkinson from Tolmar. Stuart can pound the golf ball. He can also three putt very well as well.

STUART ATKINSON, MD: Okay well thank you very much for the opportunity to speak to this very august body. Yesterday and the day before I heard so many people saying they've been to this meeting 10, 12, 14 times. Well this is the first time I've had the pleasure of being here, and as you'll see my company has only been in existence for just longer than a year. But I hope that over the next 14 years we'll continue to meet and I can continue to come back.

DR. CRAWFORD: Absolutely.

DR. ATKINSON: So I'm the head of medical affairs at Tolmar. I've just been there for four months after a little stint with my friends at Medivation before that. I'm just going to try in ten minutes to tell you a little bit about Tolmar. Most of this has already been mentioned previously today and yesterday about the new data about less than 20 and orchiectomy. Some data on getting to less than 20, a little bit about my product Eligard and Atrigel technology and a little bit at the end about the Eligard clinical data.

So Tolmar is a new commercial entity in the U.S. We are dedicated to urology. Currently we just commercialize one product but hopefully that will change in the future. We're based in the Chicago area, in the same part of the woods as my friends at Estellas and Takeda and Abbott, AbbVie.

We have a development and manufacturing capability not far

from here in Ft. Collins. And Tolmar is the inventor, developer, and global manufacturer for Eligard. And we as a new company are really committed to play a role in advancing the science in advanced prostate cancer and LHRH agonist therapy.

So as was mentioned earlier today 50 years ago when surgical castration became the treatment for advanced prostate cancer at that time the assay showed that testosterone got to less than 50. And recently some more studies have been done and some statements to say that was old science and what is the new science we know today? And there were, there have been five papers over the last few years taking surgically castrated men and measuring their testosterone under new techniques with new assays. And as you can see today's assays show that testosterone should be down to 20 if you're trying to get a testosterone to the same level as a castrated man.

And as you heard earlier a number of studies are now being done looking at the clinical benefits of getting down to 20, both in terms of delay in disease progression or in terms of improved survival. And these six studies have been done over the last eight or so years, either retrospective or prospective looking at either delay in disease progression, or survival, or both. Looking at generally a target of less than 20. One of them, the Dason study was looking at a figure of 32, and all of these studies showed a benefit to the patients in getting to less than 20.

And the next few slides just give you a bit of data to those studies but I think they're well known by all of the experts in this room so I don't want to go into great detail. But here's the Morote study. Here's the Perachino study showing a five-year survival advantage. A second Perachino study showing that PSA, Gleason scale, and age all were relevant but so was six-month testosterone. The Dason study I mentioned. The Bertaglia study again looking at patients 20, 20 to 50, and above 50. And probably most importantly because it was the most recent one is the Dr. Klotz study again showing benefits in getting down to less than 20.

So that's the new data that's come out. But how is that impacting upon both clinical practice but also the

guidelines which guide clinical practice. And you look at the NCCN guidelines which are some of the most commonly used, and previously they actually included a target of less than 20. But not it actually says adequate suppression of T is desired at less than 50. But it says an optimal level has not been defined. So that group has not yet changed their guidelines to think about less than 20.

The ASCO and AUA guidelines make no mention at all about what level of testosterone you need to achieve, but the AUA guidelines and the most recent version they have now included a statement about less than 20 ng/dL as being the definition of castration. But they include a note that there is a lack of definitive data about it. So we have discrepancies between the guidelines which the conditions are following.

So as you all know we make Eligard and we have the Atrigel technology, which is the mechanism by which leuprolide acetate is released following a subcutaneous injection it forms a solid implant which then releases drug over the duration or action of the particular dosage. And as you know you have a number of drugs to choose from in this space, either leuprorelin, or triptorelin, or goserelin, or Ferring's Firmagon. This slide just emphasizes some of the differences between them in terms of administration, needle size, injection site, and approval dates. Many people don't realize Eligard actually was the first six-month formulation developed in this space. But you have many different options to treat to reduce testosterone in patients with advanced prostate cancer.

And lastly, a little bit about the Eligard efficacy. So this slide just shows you over six months how we get down to serum leuprolide concentrations which from the literature are those which are needed to suppress testosterone. So we get good levels over the six-month period.

And then as you know with all of the agonists you're going to get the peak to start with, but with all four different dose strengths you can see you get down to below 50 by three weeks. And our mean data are shown there, maintained through the first few weeks. And then this shows in study using multiple doses getting out to a one-year period. And

you can see all of our doses get down with a mean of around 10.

And if you look at the percentage of patients which get down to 20 by week you can see that more than 90% of patients get down to 20 by week six and are maintained throughout the dosing interval.

And lastly and importantly the adverse event profile of these products are well known but this slide just emphasizes those malaise, fatigue, weakness, hot flashes, of course effects on bone, and we know about tumor flare, hyperglycemia, cardiovascular disease, and the contraindications in terms of hypersensitivity and pregnancy.

So that's my quick review of my company and Eligard. I would be happy to answer any questions.

DR. GARNICK: Go back to your--[Applause]. Going back to your slide on testosterone surge with the different formulations.

DR. ATKINSON: If they can take me back--

DR. GARNICK: Three back, three back.

DR. CRAWFORD: It's actually an interesting slide. I saw that several months ago they put it together.

DR. GARNICK: I'm actually every surprised to see that data because my impression was that based upon our own experience and FDA regulatory experiences that the magnitude of the T surge is clearly proportional to how much peptide is released in the first week and I'm not aware of, I mean I don't think that data exists for Lupron. So that's just a comment. I'm just really surprised to see that the magnitude of a T surge is no different if you're giving 7.5 mg versus giving 22.5 or 30.0 mg.

DR. GOMELLA: But don't you saturate the receptors and it doesn't matter after a certain amount?

DR. GARNICK: You do but it takes a few weeks to do that so but the receptors are virginal at the very beginning, the first dose.

The other question that I have is do you have any data on acute on chronic after each of the dosing formulations when

they're given subsequently? Do you have any - - ?

DR. ATKINSON: So I don't have that, of course these are just mean graphs so there may be a patient in there who does have an acute on chronic spike but I don't know what percentage of those--

DR. CRAWFORD: We actually, I published the six-month data. Okay? So it was six month but it was a year study and in the paper people were re-injected at six months and to my knowledge there weren't because the tail, the tail on Eligard is actually very good. It's way beyond six months. Right? It's almost beyond seven. So you don't have the naked receptors where you get the acute on chronic that you see. And I don't think we saw any.

DR. GARNICK: The only practical comment I would say is that the one-month is really not a one-month depot, these I'm talking about Lupron. I can't talk about Eligard. But so I will, you know, at least five to ten times a year I'll fight with insurance companies because I only use the four-week depots. And the insurance companies will say well that means 13 doses in a year as opposed to 12. And likewise the three-month depot is not a three-month depot, it's a 12-week depot, and a six-month depot is not a six-month depot it's a 24-week depot.

DR. GOMELLA: But you don't know that.

DR. GARNICK: Well I do.

DR. GOMELLA: That's not, okay, the only six-month depot out there is this one until Lupron came out and it took them a decade to get that stuff on the market.

DR. GARNICK: But is the label at 20? Is the label at 24 weeks or is it six months?

DR. ATKINSON: It's a very interesting point. The label for all of these products are they say six months and all of the approval studies are done at 24 weeks.

DR. GARNICK: Right, that's exactly right.

DR. ATKINSON: So you need to do the study longer and show what the levels are to prove that your product extends to the full--why did the FDA do that? I have no idea. I think it's--

DR. GARNICK: But the studies are done with basically in four-week intervals but the label rounds it off to one month.

DR. ATKINSON: Correct, and the strange thing is the insurance companies won't reimburse you for a second six-month dose until you get to 26 weeks.

DR. GARNICK: That's correct.

DR. ATKINSON: Even though technically the efficacy is only proven to 24.

DR. GARNICK: And the last practical point is that at this conference I presented data at least on two or three separate occasions in which you're dosing patients with these agents based upon, they're not based upon body weight, they're not based upon adiposity, they're not based upon body surface area, they're not based upon body, you know, BMI. So to me I'm very, very cautious when I have a relatively obese patient, someone over 100 kg that's getting the same dose as someone that weighs 50 kg, and the people that are not suppressing not uncommonly, and again I'm using only the four-week depot, will actually have tremendous responses in terms of testosterone and PSA reduction if you go from every four weeks to every three weeks in the - - .

DR. FINKELSTEIN: So they must have that data. Right? They must have what the - - people weighed? Right? I mean you could break that slide down by weight.

DR. ATKINSON: Yes, so we could obviously look at every individual patient and see where they were suppressed to and you can track that against exactly those things you mentioned; age, weight, and--

DR. FINKELSTEIN: If that was true then a typical 70 kilo guy right? Would be fine but the--

DR. GARNICK: That's correct.

DR. FINKELSTEIN: But they have enough, I think they have what? 400 patients or you should have enough patients.

DR. ATKINSON: So obviously the studies were done a long time ago. I wasn't there at the time but the FDA would normally, they have to do a covert analysis to see whether age, etcetera affects your data and I don't know whether

that was done.

DR. GARNICK: They never, they have never looked at weight as a variable. The other issue with Eligard that may be less problematic than with an IM injection is that with the IM injections you're basically using a needle that's a certain length and sometimes what you think is an IM injection may actually be a subcu injection for a formulation that's intended to be IM. You're not going to have that problem with subcu injection with Eligard.

MALE VOICE: Nice talk. At least Takeda knows the weight data because when the one-month formation was launched in Japan it was half the dose of the U.S. dose which has been approved several years earlier.

The comment, so 20 ng/dL--

DR. CRAWFORD: Can I just, Michael one second. Okay? Zoladex, Lupron, - - outside of the United States to my knowledge all of the LHRH analogs are based on essentially half the dose that Lupron is based upon, and the reason why Lupron is 7.5 mg as opposed to 3.6 mg in the United States is because way back when when Mike and I were doing the Lupron studies we basically, the therapeutic index was so marginal, I mean there was just no toxicity according to the peptide that we actually made the recommendation to TAP to put basically double the dose of Lupron for the depot to avoid the late, the late escapes from testosterone suppression.

DR. CONCEPCION: Okay good point but--

DR. CRAWFORD: Nothing to do with--

DR. CONCEPCION: But back to the all important 20. First of all, it's probably irrelevant because I suspect no one is going to come up with another drug for primary castration again, and it was an FDA thing at 50. But it's good everyone knows that. But there could be a more interesting thing and that is to my knowledge no one has tried to put forth a potential advantage to their compound in a more effective lowering of free T. Now we have very reliable assays for free T as opposed to when Mark started. And it's obviously the much more important molecule. So why is nothing, to you or anyone on the panel, why has no one jumped on that bandwagon?

DR. CRAWFORD: Well you were when you were at GTX but it never went anywhere.

MALE VOICE: I know but we didn't, I mean that was only a part of it but I mean it should be--

DR. CRAWFORD: But you were with GTX.

MALE VOICE: With every drug. You could say Eligard could lower the free T for all we know. I mean we don't know.

DR. CRAWFORD: That's why some people use Eligard with hormonal therapy. All right. I think we need to move on.

DR. ATKINSON: Okay, thank you.

MALE VOICE: Okay, thanks Stuart.

DR. ATKINSON: Thank you.

DR. CONCEPCION: Let's see, the next speaker will be Joy Zhu? From Bavarian Nordic, and as many of you know they have a therapeutic vaccine for prostate cancer called Prostvac that just accrued their phase III in their PROSPECT trial.

JOY ZHU: Yes.

DR. CRAWFORD: I didn't look and there were questions. What do you see happening in the future in regards to tracking T levels and formalizing less than 20 as a target? If you look at the PDR it tells you to track T levels and a lot of people don't. I think if you do you'll be surprised and I encourage people to do it. And so what do you do, the question is do you track, what if they don't reach a level of less than 20? What do you do Dr. Garnick?

DR. GARNICK: I've got to tell you the number of patients that I have that don't reach less than 20 who are not obese who are getting q. 4 weekly Lupron it's anecdotal.

DR. FINKELSTEIN: Okay but you do see people in second opinion--

DR. GARNICK: Yeah.

DR. FINKELSTEIN: That were on three-month depots or four month that in fact you already said--

DR. GARNICK: I'd change them to one month, I'd change them to four weeks.

DR. FINKELSTEIN: You don't do bilateral works on them or anything?

DR. GARNICK: No but then, and if they're still, if they're still above 30 I'll basically go to every three weeks.

DR. FINKELSTEIN: Okay.

MS. ZHU: Hi I'm Joy. I want to thank you David for inviting me to give a talk. So I'm the Vice President of Development for Oncology at Bavarian Nordic. I joined this company in February so I'm fairly new but not new enough to claim that I don't know anything about it yet.

So just to give you, not many people know our company. So Bavarian Nordic is a multinational company. The platform is considered, it's vaccine-based immunotherapies. So one part of the company is in infectious disease and its R&D is located in Munich, Germany, and the other part of the therapeutic area is cancer, which is located in California in the Bay Area. The headquarters and manufacturers are outside of Copenhagen, called Kvistgaard.

So the company was founded in 1994 and is a public company, publicly traded in Denmark. So we right now the market size is about six billion dollars in the company and we have collaborations with BMS on product options licensed -- and we also have collaborations with J&J and in the development of the Ebola vaccine. In addition to that the company produces for biodefense produces smallpox vaccines for U.S. government and many of the development companies around the world.

So let's talk about pipelines in cancer in particular. As we touched on slightly today and yesterday we have a drug prospect which is fully enrolled in phase III in castrate-resistant prostate cancer, metastatic. So with that, I will get into details in that.

We also have another vaccine called PANVAC which also is in clinical development utilized in MUC-1 and CEA as a tumor-presenting antigen. The other drug that is in our pipeline is also in clinic, that NCI is leading the phase I study in all comers. It's called Brachyury. With Brachyury not many people know is a transcripter factor. It's involved in more advanced solid tumor cancers, especially in resistance, chemo-resistant tumor types, and lung,

colorectal, breast cancers, other ovarian or advanced cancers have highly expressed in Brachyury. So we're also in development of that. In the interest of this group I will not talk about PANVAC and Brachyury.

So our platform is cancer immunotherapy is consistent. So our drug is different from Provenge. Our drug is an immunotherapy that consists of heterologic, or recombinant immunotherapy that consists of poxvirus, that - - carries transgenes of tumor antigen, in this case for prostate case is PSA. In addition to that we also have a triad of co-stimulator factor that stimulates T cell responses. So for our vector the way that this drug works is, I'll get to the next page, so the way this works is the first administration is a priming using Vaccinia for Prostvac. So that's stimulated innate and adaptive immune response. Vaccinia and fowlpox vaccine, fowlpox vaccine is used for boosting. Both vaccines consist of PSA as well as the TRICOM, the - - stimulated factors that generates long-term memory T cells and also when T cells and tumor cells and dying tumor cells produce more tumor antigen that generates cascade, antigen cascade effect. So we're thinking, our job is the immune response is not, it's durable. So priming is provoke immune response by using boosting doses that will generate memory responses, and then create, and in turn creating antigen cascade.

So in the clinic what Prostvac is given is one dose, oh so one back, so one dose of priming and two weeks later followed by every two weeks of dosing for up to week 11 of boosting. And after that is three doses of every four weeks of dosing, total of 21 days of dosing for Prostvac. After that we follow in long-term, just long-term follow up.

I'll talk about that study design. So one of the hypotheses is talking about tumor growth. Tumor growth is a very dynamic effect in itself. What we talk about here is the hypothesis, and this a paper published in clinical cancer research by NCI James Gulley and his team. So usually tumor growth it consists of a tumor volume growth that has tumor cell growth as well as some of the dying cells. And when giving chemotherapy that chemotherapy will be able, can shrink the tumor and create a tumor volume reduction. Vaccine treatment normally don't kill, directly kill tumor itself but it creates a slowdown of tumor growth

rate. So therefore one of the discussions that we just had is saying that for immunotherapies, especially for vaccine, is much better for us to get an earlier disease so that the patient had enough to change the course of tumor growth versus of really causing a tumor reduction, especially in the metastatic disease setting.

So when we combine with our vaccine in chemotherapy or with immune checkpoint inhibitor which we have the data showing is chemotherapy or immune checkpoint inhibitor can create tumor size reduction. When adding our vaccine to it, it will change the course of tumor growth in return. So therefore by doing the combination even in late state we anticipate to see tumor growth rates change that could potentially see tumor reduction when in combination, but more importantly to showing an overall survival benefit, may also have some progression-free survival benefit.

The hypothesis actually led to our randomized phase II study that was published already that's showing the results. One slide that shows that, so this is the prospect - - . We talk about the PSA antigen tumor presenting, tumors, PSA tumor and antigen as well as the TRICOM here. So what we showed in the randomized phase II study that published here is that looking at PSA itself the growth rate and looking at PSA doubling time compared to the placebo group, which has from the beginning of randomization, at the beginning of randomization of 4.4 at entry, and we were able to slow the tumor growth rate to a PSA doubling time of 7.7. This trial alone also led to the potential or the trend of showing a median survival benefit. Obviously this study was done a long time ago but you can see the median time to progression of 25 months probably right now is abiraterone is actually less than that but this study was done a long time ago. But comparing to placebo we do see a big difference of about eight months treatment difference. So this study, the PROSPECT study, actually led to the randomized phase III study design which we'll talk about in the next slides.

In addition, currently this year NCI actually published, presented this data, PROSPECT, in combination with ipilimumab, which is a CTLA-4 antibody in prostate cancer that showed a median survival. This is a single-arm study, a very limited number of survival, about 32 months. This is new data, you know, small phase I study in those two

doses, and so you take it as what you can. But we have seen some synergistic effect.

So what PROSPECT has positioned is this group for the phase III study and that fully enrolled is in minimally symptomatic, castrate-resistant, metastatic prostate cancer so in the curve that you can see. So this is a phase III study double blind, a global phase III study. We actually have three arms in this. One of the reasons that we started this study had three arms was one arm we're using Prostvac in combination with GM-CSF in the study based on the phase II data. But we weren't really sure. There's not enough data to say that without GM-CSF it would not work so we have another arm just Prostvac alone as compared with placebo. So a three-arm study, the comparison for it so primary endpoint is survival, so the comparison is Prostvac plus GM-CSF compared with placebo or Prostvac compared with placebo. This study was under agreement with FDA under SPA, and is fully enrolled. So treatment is six months and then followed by long-term follow up for survival. So we started the study, the enrollment in January of 2011. We were finished in enrollment at the end of last year. All patients are now in long-term follow up. The events rate as you can tell, you know is not that high and is based on all of the treatment available. So we're still waiting for events to occur probably sometime next year.

One of the key follow up items here is to capture patients post-treatment anti-prostate cancer therapy because we believe a part of immunotherapy it is critical for us to capture all patients post our treatment and seeing the multiple potential immune, long-term immune effect. And so we're hoping that we'll get the results next year.

So the other thing I wanted to talk about Prostvac the drug is in huge collaboration with, it was NCI and - - . We have lots of studies sponsored by NCI that captured really the span of the prostate cancer therapy from early stage to late stage. There are many smaller studies that are being done in adjuvant setting, neoadjuvant setting in combination with abiraterone and enzalutamide as well as with radium here. And that's in pre-clinic. We're planning to move into clinic as soon as we get preclinical data.

So I think this is my last slide. Thank you. [Applause]

DR. CRAWFORD: That was a great talk. So did the Prostvac trial hit its target accrual?

MS. ZHU: Yes. We actually accrued, the study was 1,200, we actually over enrolled to just under 1,300. The reason for that is there are a couple of sites in Germany were starting really late because of all of the issues that we didn't want them to not be enrolled. So we actually opened the enrollment, waited for them to enroll, and then we closed it.

DR. PETRYLAK: How were you dealing with the issues of post progression therapies?

MS. ZHU: So we're required all sides, every patient to be, to capture post treatment, you know, progression, post-treatment progression or any time progression. So we're capturing the anti-prostate cancer therapy with the date and the therapy they're getting.

So what kind of analysis that we're going to do in the end we have to see the results. But we're thinking that most of the patients, so for vaccine if you get active vaccine the immune response could really add synergistic effects for other therapies. So if you are on the active arm potentially other enzalutamide or docetaxel would potentially prolong their treatment effects. So we're capturing that so hopefully we can do analysis on that.

DR. GARNICK: Okay, just a point of caution. I understand you're not dictating what the progression therapies will be at the time of progression post-Prostvac.

MS. ZHU: Correct.

DR. GARNICK: Okay, that's a potential problem, that could potentially be a review problem for the FDA at the time of considered approval because you don't want to have an imbalance of one arm getting great therapies such as second-line abi, enzalutamide, chemotherapy that's not balanced among the other two arms. And the perfect example of that is tivozanib that was used in kidney cancer in which the post-therapy progression was not dictated and tivozanib is a terrific drug but it did not get approved because of that study design.

DR. CRAWFORD: Why would you think this wouldn't happen there in sort of a randomized trial where people were sort of the same in the community?

DR. GARNICK: It totally depends upon the geographic area that the study is taking place in. So for example, if you've got a lot of Eastern European countries where these second-line and third-line therapies are not available you're going to have a huge imbalance. So in the tivo, in the tivo study it turned out that the majority of those patients came from Eastern European areas where they did not have second-line sunitinib, pazopanib, and the whole series of the other TKIs. It was basically the, one arm had essentially 63% of patients getting appropriate second-line therapies and the other arm 12%.

MS. ZHU: Yeah, I think that's actually a good point. We are, obviously now it's a blinded study and we do have Europe, Russian, and a couple of Eastern European countries as well as Germany and others. So we can see that the post-treatment anti-prostate cancer therapy in Europe more of docetaxel. In the U.S. enzalutamide and abiraterone are kind of balanced here but we don't know the breakout between the - - .

DR. GARNICK: Yeah, but I'm telling you it's going to be a real problem is this goes to an advisory committee because you're going to have, let's assume that either of the GM arm, the GM or without the GM show improvement you're going to look at what the progression therapies were in that patient population and the results are going to be completely confounded.

MS. ZHU: Yeah it could be but I don't know whether it would not be balanced because I would think that if we balance the region then the regions in therapy should be similar.

DR. GARNICK: Good luck.

MALE VOICE: Did you not have - - geographic distribution as well as stratification criteria?

MS. ZHU: Yeah, I think so. I think so the balance--

MALE VOICE: So that should help.

MS. ZHU: Yeah, that's what I'm saying. Yes.

MALE VOICE: But you know, the problem would be is in Eastern Europe where you may get one subsequent treatment here in the United States you may get four, however you may actually skew it in Europe, that you'll have a better survival benefit because of the fewer treatments that are available. Yeah, I think that there are a lot of, there are multiple ways this could be looked at. Certainly Takeda ran into the same problem, at least it looked that way in their second trial, their first trial, excuse me, the post-docetaxel trial. It turned out the drug was not a good drug and in the pre-chemotherapy trial you really did see the difference. I think that this is going to be, it's going to be a very difficult area to--

MS. ZHU: Yeah, I 100% agree with this.

DR. GARNICK: What are your eligibility stratifications as well? Are you stratifying patients by number of previous therapies before they became castrate resistant?

MS. ZHU: I don't think we stratified based on that. It's a treatment naïve metastatic--

DR. GARNICK: Are treatment naïve.

MS. ZHU: Yeah, yes, treatment naïve, so that part is not but as far as stratification I think it was really by the region, not to my knowledge of anything else. So it should balance a little bit.

MALE VOICE: Okay.

MALE VOICE: Another argument is if you believe this is a prolonged activation of the immune system with T memory cells developing over time it's probably not going to make, it will make a difference in the overall survival but you may be able to get away with it. As something like tivozanib, which was a drug that was either yes or no and there was no subsequent issue. So again, I think this is the complexity of immune therapy when you're activating the immune system for a long period of time we're just going to have to see what the data tells us.

MS. ZHU: Exactly. Well think you.

DR. CRAWFORD: Joy, thanks. Okay so we've got what two more speakers? So the next will be Jim Caggiano from Valeant. As you know Valeant took over Dendreon a few months ago so

I think Jim is going to give us an update on what's happening over there.

JIM CAGGIANO: Thanks doc, hi everybody. You know, again I want to thank you Dr. Crawford for having me back here. I was, as some of you know I was at Dendreon from 2004 to 2008 and when we filed with the FDA the first time and got the complete response letter. I left shortly after that and was recruited to Allergan to move to Newport Beach and run a different business. That's what I did.

DR. CRAWFORD: Botox?

MR. CAGGIANO: No, actually it was the lap band for morbid obesity, not quite as fun as Botox, but Newport Beach is great.

DR. CRAWFORD: A lot of Botox there.

MR. CAGGIANO: Yeah, that's right. So at any rate Dendreon went bankrupt as everybody knows, and I'll talk to you a little bit about that. Valeant bought them out of bankruptcy and then Valeant hired me back to run the business in the end of May of this year. So just sort of safety disclaimers.

So Dendreon went bankrupt more for financial issues than for operational issues, although as was alluded to earlier in my opinion they sort of blew the commercial launch. I think the trajectory of performance commercially would sort of reinforce that. When I was there the plan was to do pretty much what Lupron depot did. I mean we had a lot of success at TAP where I ran Lupron in the late 90s. You know, really kind of catering to urologists versus trying to get the patients in oncology. And if you look at what Zoladex did they sort of took the other tack and the relative market share sort of spoke for themselves as we sort of wiped them off the face of the earth.

So anyway, Dendreon had 622 million in long-term debt that was due in 2016. There was no way they were going to cover that. Financial restructuring was approved allowing for the sale of the company. There was a voluntary chapter 11 and the whole time there was no disruption of the business, so you guys who are familiar with Provenge and have used Provenge likely noticed no disruption during that time.

February 2015 Dendreon buys them. It's Valeant's first

sort of foray into the GU space. Provenge remains commercially available today. All of the customer programs and agreements continue. There's no disruption to the business and now the strategy, as it probably should have been at approval in 2010, a real deep focus on urology, particularly in the community. And the academic centers is a little bit different because there doesn't, there seems to be a lot more cooperation in the academic centers than there is in the community for whatever reason.

So who is Valeant? Multinational pharmaceutical company, the market cap in 2008 was about a billion dollars. Yesterday it was 84 billion dollars. So that was a pretty good stock to buy if you got into it in 2008. Diverse product portfolio they've executed over 140 business development transactions since 2008, various products, various companies. We're organized into seven different business units, and I obviously run the urology oncology portfolios. So in addition to Provenge and trying to grow that business organically we're always looking for acquisitions and co-promotions either in urology or in oncology.

So I can go through these fast. Right? Because between David and Steven and Dan and Raoul I feel like it's all been covered. Right? So one of the problems when I was at Dendreon the first time especially in 2005/2006 we were talking to folks about immunotherapy and they were like what? You know? What is that? What do you mean there's no PSA response? This is not what we're used to, and there was a whole lot of skepticism about whether or not it was real medicine.

Fast-forward to today where there's all kinds of immunotherapies and it's in the press all the time I think that sort of, we're past that point. But when people are talking about hey these things are the future of cancer therapy well the future is already here. Right? And it's been here since 2010 because as somebody said earlier Provenge is a personalized immunotherapy that has shown a survival benefit.

So we saw this slide, a lot of these slides get amortized I think across the companies. The idea is immunotherapy in particular seems to work better when the tumor burden is less.

This is the Provenge graphic, right? Provenge activates the T cells, the T cells proliferate and attack the cancer cells which express PAP. What's not on here is that then you have this antigen cascade or antigen spread which gives you further efficacy.

So the theoretical model suggests that immunotherapy may slow the tumor growth, that it works a little bit differently, activating the immune system and elicits an immune response, and many immunotherapies have demonstrated improved survival without showing an impact on the traditional markers, like in this case PSA.

Here is the trial, as somebody said, I think it was Dan, if you were designing this trial today you'd probably do it a lot differently, but it was designed a long time ago, a lot of problems with how it was designed yet it still showed a survival benefit, which I think we're all familiar with 4.3 months at the median. But the thing to remember here is the median PSA of the patients in this study was something like 55 or 56, one of the clinicians probably remembers the exact number better than I do, but a lot of these fellas are pretty sick by the time they're enrolled in the trial. And like was alluded to earlier when you cut this by quartiles the patients whose PSA was less than 20, or I think maybe it was 22 the median benefit was something like 13 months. And today in practices that actively surveil their patient base and use Provenge regularly. They're catching patients with PSAs less than five and starting them on therapy. And anecdotally of course, because that's all they have, these guys are living a long time and doing really well.

Here we have a percentage of folks alive at three years. So there were some patients who were followed up beyond three years, but to Dan's point not a lot. We see some improvement at the four-year mark, and then obviously the side effect profile is very, very manageable with Provenge, not like you see with some of these other therapies. In fact, it's nothing that precludes you from adding on or layering on other therapies down the road. Right?

So a lot of folks talked about sequencing treatments in this patient population, or now it seems to be more popular say layering or matrixing or whatever. These are the old NCCN guidelines in 2014, and you have sipuleucel-T reserve

back here, sip-T or Provenge is not in the front line and when the guidelines were ratified they moved it up here. Does this thing have a laser pointer on it?

DR. CRAWFORD: There should be one up there.

MR. CAGGIANO: Oh yeah, this big thing. Right? So sip-T is now up here in front-line therapy. So this is a pretty big deal for us. I think that we're excited about that, trying to get this word out that when these guys are in the space, which metastatic, asymptomatic, or mildly symptomatic where they're not on opioids sipuleucel-T should be the first line of therapy that they encounter. And frankly what a lot of, what a lot of practices are doing now even if they weren't, if patients happened to be on either Zytiga or Xtandi they're calling these patients back in and evaluating whatever or not they're still on label for Provenge, and if they are many of them are starting on Provenge because the unique thing is that if you look at the label for Zytiga, and maybe this is a question for you Dr. Crawford, right? The label between Provenge or sipuleucel-T and either Zytiga or Xtandi is not that different. Right? In terms of the patients that it covers.

DR. CRAWFORD: Yeah it's a little different. I mean yeah I mean the no pain thing, the lymph node differences. I mean that's with radium and so forth.

MR. CAGGIANO: Okay well what we wrestle with--

DR. CRAWFORD: - - .

MR. CAGGIANO: Yeah, what we wrestle with is there's probably 4X the number of patients in the United States who get treated with one of those two medicines than who get Provenge, and that seems a little disproportionate.

DR. CRAWFORD: It is.

MR. CAGGIANO: Yeah. So that's what we're trying to turn around now.

DR. CRAWFORD: The question is why.

MR. CAGGIANO: Well I have my theory but it's more important to hear what the guys in the audience think. Right? I think what Dan said earlier is a big part of it. I mean--

DR. CRAWFORD: No, I mean you've already said it. There are so many things. I mean the political stuff, and people were angry, the PSA stuff, the cost stuff, the I don't make people sick and it's not chemotherapy stuff. Just a lot of things.

MR. CAGGIANO: Yeah, I mean I can tell you anecdotally--

DR. CRAWFORD: We don't think it works, the trial, they were foiled, their data, there are a whole bunch of different things. We've all heard it. Dr. Garnick is going to say something now. Right? No?

DR. GARNICK: I've had patients that have had Provenge and have brought their hospital bills in to me and at academic institutions that send their patients, that either do their pheresis or send their patients out to the American Red Cross the per pheresis cost has been 71,000 dollars that have been reimbursed by insurance, making it to close to 231,000 dollars. So what is sort of the nationwide pheresis cost for giving Provenge?

MR. CAGGIANO: I don't know. We pay them like 800 dollars per pheresis that they do for us. So I don't know what's going on there.

DR. VESTAL: We don't get, I mean ARC does ours and it's part of that.

MR. CAGGIANO: Yeah, all the apheresis is covered as a part of our cost of goods, which is why it's, making this, one of the reasons this is as expensive as it is is this is not pills in a bottle because we pay for the apheresis, the transportation, the transportation back, that's all part of cost of goods. So I can't imagine how--

DR. GARNICK: But you must have some information on what hospitals are charging.

MR. CAGGIANO: I don't know why the hospital is charging anything for the apheresis because I'm paying for that to be honest with you.

DR. FINKELSTEIN: So can I ask by a show of hands--

DR. CRAWFORD: Well let's solve this because Marc I've heard you say this a bunch of times.

DR. GARNICK: I'll show you the bills.

DR. CONCEPCION: That seems inappropriate.

DR. CRAWFORD: So what I'm hearing Jim say and I hear Raoul say it's all part of the package.

DR. CONCEPCION: Yeah, that seems inappropriate.

DR. FINKELSTEIN: So can I ask by a show of hands?

DR. CRAWFORD: No, we're not done with this yet.

MR. CAGGIANO: I can tell you what our wholesale acquisition cost is per infusion for the whole thing is 38,000 dollars.

DR. CRAWFORD: Does our hospital bill more? You know they inflate everything. They charge what is it? 2,000 or 3,000 for a one-month Lupron injection.

DR. GARNICK: My hospital one of my patients who was on the original trial was able to get "booster shot" of Provenge and my hospital charged 105,000 dollars for one pheresis.

MR. CAGGIANO: Well that's, and I would imagine that did not go through insurance.

DR. GARNICK: It did.

MR. CAGGIANO: Well I'm surprised insurance paid for it. I mean--

DR. CRAWFORD: So if they're paying, 60 Minutes actually did a little gig on this last year on what people were billing and stuff like that. Yeah, I know our hospital over bills everybody because once in a while they hit and they collect and then, but most of the time it's what Medicare pays. What does Medicare pay? I guess that's what--

MR. CAGGIANO: Medicare pays the average selling price plus 4.3%

DR. CRAWFORD: Steve, what were your comments?

DR. FINKELSTEIN: Well I wanted to, I was kind of going along with what you said. I wanted to know from the clinical physicians in the audience how many of you are actively giving Provenge currently. A show of hands.

MALE VOICE: Most of the - - groups. Isn't that right Raoul?

DR. CONCEPCION: I don't know about most.

MR. CAGGIANO: I don't know about most but a fair number of

them. I mean we've been--

DR. FINKELSTEIN: It's too hard for a single practitioner, a big old - - group or something to get into but--

DR. CONCEPCION: I mean we've treated close to 150 and Marc I mean ARC does ours, they never set foot in the hospital and as far as I know the American Red Cross has never billed the patient directly for pheresis.

MR. CAGGIANO: Most patients pay less than 50 dollars out of pocket for the whole thing.

DR. FINKELSTEIN: So my corollary was for those of you who didn't raise your hand, along with what Dave said, what is the impediment that causes it? Is it something that you were saying or is it something else?

DR. GARNICK: My impediments are I have no idea what the drug is doing. Okay? So there's no PSA response, there's no anti-cancer response, and I've also had patients come to me that have had really exacerbations of the disease after receiving Provenge. And whether that's true and unrelated I don't know but I have no handle on what the drug is doing before I got to the next step.

DR. FINKELSTEIN: Okay so going along with that, so I just told you I gave a guy Provenge. I took a scan beforehand, I gave a scan afterwards and his disease went away.

So going along, so for those of you who don't give it what is the, so you again said PSA I can't follow. I get that. But the other part if you use current imaging you could use this in the way you use everything else.

DR. GARNICK: But there's not objective response data that was part of the study.

DR. CRAWFORD: Living longer is not an objective thing?

DR. GARNICK: I'm not going to get into those particular details. I'm just saying--

DR. CRAWFORD: Well what are you talking about? I mean a lot of things we do, I mean have no objective response that--

DR. GARNICK: So give me a mechanism of the PSA not doing anything, no anti-cancer objective response if the patients are living longer.

DR. FINKELSTEIN: So radium doesn't knock your PSA down and we see objective responses and people live longer. I mean the issue is that today, you know, the problem is is they were the first ones in the space. We didn't have the fancy imaging to basically look. So if you want to use PSA as the way to keep track of people you were screwed. But today you can. And so if you didn't believe in Provenge you can test it. You can give Provenge and see if it actually goes down. Look at their disease burden.

DR. CRAWFORD: So Marc, there was a study with radicals. Is that what you were going to say? With the tumor, the infiltration.

DR. PETRYLAK: This is something different. Make that point and I'll make mine afterwards.

DR. CRAWFORD: Nah, the study in the pre-radial high risk where they got sipuleucel-T they took the prostates out and they saw a tumor response, they saw infiltration around the tumor. What was it?

DR. FINKELSTEIN: T cell infiltrate from - - .

DR. CRAWFORD: Yeah, compared to people that didn't have it, and people that had hormone therapy they didn't see it because they combined it with hormone therapy. I mean that's a response. I mean that was, and then plus you get up regulation of all of these things that supposedly do something, immunological responses. And what were you going to say Dan?

DR. PETRYLAK: Well, I think the whole problem here is the failure of the company to publish their data, the subsequent analyses of what went on with Provenge. So number one, we published within the last year a study that looked at the time to the development or the initiation of pain medications and subsequent use of narcotics. And we found there was a significant difference in pain progression as well as the use of narcotics in favor of those patients who received Provenge. I think that's indirect evidence. I mean again it's not direct but it's indirect.

The second issue has to do with kinetics. If you look at the IMPACT trial it takes about six months for the treatments to change, and you're going to give one month of

treatment and then patients often went on to something else after that. If there was a delayed effect, if there's a bent arrow effect in other words, if it takes time for T regs to turn themselves on or T memory cells to develop that window, people go on other treatments. So you may have lost your PSA response. It may not have happened immediately. But Medanan [phonetic] and his group at the NCI have looked at this in terms of vaccines. You have the same issue with Prostvac. And Prostvac showed the same thing. They showed no change in time to progression, no PSA response rate, but their randomized phase II, albeit a randomized phase II, did show something.

So I think that with these vaccine-type treatments this may be what happens. It may not be the same thing for CTLA-4 or for checkpoint inhibitors. Again, part of the problem is that fact that these things were not designed into those trials initially, but that's sort of the way I look at it, that's the way I justify the use.

MR. CAGGIANO: Yeah, and just another thing on the phase II, the reason I was chuckling is because Dave you said it was heresy, but there was, there was a phase II that in biochemical failure after radical where the PSA doubling time in the Provenge group was something like 48% longer than the PSA doubling time in the control group. Right? Again it's not survival but it looks like it's pointing in the right direction.

And I can tell you commercially from when I was there the last time, and it hasn't changed much from now, there are two camps. There are people that just don't want to believe and you can point to a million different things, the trial was bad, the n is small, those are subset analyses, it wasn't pre-specified. But you know, if you look at the preponderance of the evidence and what people know about immunotherapy today I think it's easy to believe. Maybe I'm drinking the Kool-Aid a little bit, I'm sure I am but there's definitely a contingent of folks who don't want to believe it.

DR. PETRYLAK: And the other thing about PFS in the first trial had one patient flipped over to being positive for PFS it would have been positive based upon PFS.

MALE VOICE: That's right.

DR. PETRYLAK: So again it's just a lot of things that are pointing in one direction but it may not be, I mean I could be looking at this the wrong way but that's sort of the way I view it.

DR. CONCEPCION: And Jim don't you also, I mean you've got immune response data on antibodies and things like that. Don't you?

MR. CAGGIANO: Yeah. Yeah and again as someone said Dendreon for whatever reason didn't publish a lot of this stuff and that's a problem, and hopefully this PROCEED sort of follow-on registry we've had to do at the behest of the FDA will throw off some abstracts and generate some interest in it. But essentially we believe, as it says here, a patient is a candidate for Provenge if he fits this criteria. It doesn't really matter what he's been on before, as now the small trials have proven, as long as he's on label it's worth an evaluation. If you believe that cancer is a disease that responds to your immune system attacking it there's only one therapy out there that strengthens your immune system against prostate cancer, and everybody deserves a shot with it.

DR. FINKELSTEIN: So based on this slide, right?

MR. CAGGIANO: Yeah?

DR. FINKELSTEIN: You have to have confirmed metastatic disease.

MR. CAGGIANO: Correct.

DR. FINKELSTEIN: And that's usually on a picture. Right?

MR. CAGGIANO: Yeah, correct.

DR. FINKELSTEIN: So if you're in the audience and you don't believe Provenge works, you already got the picture, you know they have metastatic disease in order to get this thing, give Provenge and see if the thing goes away.

DR. GARNICK: As I said, I've got several anecdotes in which the disease has substantially worsened after Provenge.

DR. FINKELSTEIN: How long?

DR. GARNICK: Three months.

DR. FINKELSTEIN: Do you know the curves didn't separate until

six. The thing doesn't work at three months. If you look at three months you're not going to find it.

DR. CONCEPCION: You guys can box later. Thank you.

DR. CRAWFORD: Good job.

DR. CONCEPCION: So we've got one more because we're ten minutes behind, so the last commercial presentation will be from Kevin Baker of Metamark. Is Kevin here?

MALE VOICE: He is here.

DR. CONCEPCION: He is here. So as many of you know Metamark is another biomolecular company based out of Cambridge, and they've got the I believe the ProMark assay.

KEVIN BAKER: Good afternoon. I'm going to switch gears a little bit from pharma and other things, but I want to thank Dr. Crawford for inviting Metamark in. It's a bit of a mini Lupron reunion. Jim and I actually started at TAP Pharmaceuticals at the same time back in 1991, and I think it was about a year after they went from the daily injection to the monthly injection so it goes quite far--

DR. CRAWFORD: If you can sell that you can sell anything, particularly since Garnick did the study. Now you talk about a shitty study.

DR. GARNICK: It had at least 56 patients in it.

DR. CRAWFORD: And you're sitting over there criticizing people, a God damn study with 199 people got that drug approved. And then you had no follow-up after a year.

DR. GARNICK: - - is terrific now.

DR. CRAWFORD: And you're making fun of all of these other studies. That's the worst study in the world.

DR. GARNICK: You're an author.

DR. CRAWFORD: Not me, no, no, not me, sorry. I wouldn't be part of that.

DR. GARNICK: it's the most enduring therapy that's been used in prostate cancer for decades.

DR. CRAWFORD: And it's not, and then that's where we're finding all of the problems with it right now, about T levels

because--

MALE VOICE: Let the speaker talk.

DR. CRAWFORD: Why not use it, why not use three month and--

MALE VOICE: Let the speaker talk.

DR. CRAWFORD: Use one month that's all you'll use.

MR. BAKER: So the other quick--

DR. CRAWFORD: Marc is a good friend of mine but--

DR. GARNICK: - -.

DR. CRAWFORD: I don't have any place to stay next year for the marathon now.

MALE VOICE: There you go.

DR. CRAWFORD: I'll be staying back in the Marriott.

DR. PETRYLAK: I'd hate to see if you didn't like somebody.

MR. BAKER: Just another really quick piece of my background was a fairly lengthy stint with Alza Pharmaceuticals that brought you Ditropan XL, Testoderm, and was on the advisory board for Viadur, but I think in the late--

DR. CRAWFORD: Those are all winners.

MR. BAKER: --90s it wasn't really, the market wasn't really ready for an annual implant.

DR. CRAWFORD: That's what Bova did didn't he? Viadur?

MR. BAKER: Yeah, we developed it for Bayer at the time. Right.

MALE VOICE: Yeah, that's right.

MR. BAKER: So I'm in the--

DR. CRAWFORD: Bova messed that up.

MR. BAKER: I'm in the urology pathology services with Metamark Genetics. It's a fairly new research and development company, only been commercialized for a couple of years now. I just joined them back in November and one of the important things to keep in mind about this company is we provide comprehensive pathology solutions for both community urologists and the academic environment. Do I

have control here?

MALE VOICE: Yep.

MR. BAKER: Green button?

MALE VOICE: Oh no, no, the flipper.

MR. BAKER: Flipper? Where did it go? Oh there it is. Green flipper?

MALE VOICE: Green.

MR. BAKER: Okay, there we go. Very quickly, our product line is popping up here from ProMark, which is our first proteomic test for assessing the risk of aggressive disease for prostate cancer patients. And this is where our portfolio fits into your care continuum, all the way from screening with PCA3 and biopsies, we do prostate biopsies, cytology, FISH, and on the prognostic side ProMark, PTEN/ERG. We actually combine the PTEN/ERG. There's a fair amount of literature that powers the usefulness of combining those, and again we'll talk briefly about PCA3 after ProMark.

So this is a summary of ProMark's personalized risk assessment. It is an independent stand alone tissue test for Gleason 3+3 and 3+4, and it requires nothing other than the biopsy tissue to perform the test. It doesn't require any other parameters whatsoever which is unique to this test. The protein predictive values and the eight markers in this test are reproduced throughout the prostate gland regardless of Gleason score, which also powers the independence of this test versus its competition. There's an algorithm that also compares two of the eight markers looking at the tumor and benign tissue side-by-side, and I'll give you a quick glimpse of our technology here in a minute.

The test requires less tissue than the other markers in this space for sections of 4 X 5 sections. And it's a fully automated process, which removes the entire notion of human error. Turnaround time is about two weeks, which is the industry standard for these types of tests. And the diagnostic rate or running rate now is less than 10%, for our biopsy business our atypical rates are below 5% which is less than half of the biopsy atypical rates throughout

the country with the general reference laboratories. And we attribute that to having urology-specific fellowship trained pathology.

The other I think interesting thing to note about ProMark is that we don't grind the tissue. We retain its architecture and that's important when it comes to our technology because again as I mentioned earlier we look at tumor and benign tissue side-by-side, which we also believe powers the test.

So we've published a validation study in Clinical Cancer Research March 2015 looking at whether or not these markers can predict aggressive disease in men with 3+3 and 3+4. There were two arms of the study, 381 patients in the identification of the biomarkers and then 276 patients in the validation study. And the endpoints were distinctive in terms of favorable and nonfavorable pathology, favorably being less than or equal to 3+4, and organ confined versus nonfavorable which is greater than or equal to 4+3 and/or non-organ confined. So very specific pathology that you can take action on, and it informs on both ends of the spectrum. So the study did conclude ProMark can provide individualized independent prognostic information relative to current risk stratification systems and it may improve precision management of these patients.

This is a quick glimpse of our report, probably a little small print for those of you in the back, but essentially what we wanted to do with our reporting system is we wanted to simplify that information that we returned to the urologists. This is a sample patient with a ProMark score of 30 on a scale of 1 to 100 or 0 to 100, and the first part of the report speaks to the general prostate cancer population of 3+3 and 3+4, about a quarter of that population presents with those scores. And this particular patient with a ProMark score of 30 equated to a 15% risk of aggressive disease, so a substantial decrease in separation from the normal population. And we also provide clinical interpretation points that assist the urologist in explaining these results with their patients.

And this is an important clarification. We do provide in the report if you were to take the ProMark score and then add back in the NCCN guidelines you can further stratify your patients. The most important distinction is that you

can actually go here after you receive the score because we don't include any of that information in producing the predictive ProMark score for your patients.

The next thing I wanted to go to was PCA3 and then wrap it up because I know we're running a bit late. But PCA3 as you all know you've all touched and felt it over the last few years, many of you probably walked away from it because there was nobody promoting the product actively. We are in the final stages of acquiring the full licensing rights to Hologic's PCA3. We've actually been processing this test for about a year now and we published a Gittelman article the Journal of Urology in 2013 a study that documented a cutoff score of less than 25% being associated with an increased likelihood, or rather a decreased likelihood of a positive biopsy, and that was a four and a half fold decrease.

Dr. Crawford of course published a study for patients prior to any biopsy the following year in Urology with 1,900 patients and--

DR. CRAWFORD: 1,843 I think.

MR. BAKER: 1,843, I knew it was close to 1,900.

DR. CRAWFORD: You've got to get it right. I was correct.

MR. BAKER: But as we all know we can't overlap studies but there's about 140 studies out there documenting the utility of PCA3.

In the Gittelman study again we did replicate a lot of other previous research and showed its utility following an initial biopsy, and we're actually a little bit behind the NCCN guidelines, which is where Dr. Crawford is now, in terms of using PCA3 for initial or prior to initial biopsy and repeat biopsy. The only real implication here of course on the off label portion of it is reimbursement and with our company there's an out-of-pocket cost to patients of about 220 dollars for somebody who is prescribed PCA3 prior to any biopsy.

And just a quick reminder on PCA3 as it distinguishes itself from PSA it's not influenced by prosthetic volume. It's not influenced by prostatitis, and it is highly specific in prostate cancer. Its expression is 60 to 100

times greater in the presence of prostate cancer. And I think that's it. Short and sweet.

DR. CRAWFORD: Thank you. [Applause] And Dr. Schalken is not here but the first day he gave a presentation on PCA3 and his Quattro score and my sense was he's very disappointed about what's happened to his PCA3 since it's been taken over by Gen-Probe, Hologic, but not you. He hasn't said anything. Have you guys actually talked to me to ask him about what he thinks ought to be done?

MR. BAKER: Yeah, I'm not sure if we've talked specifically with him. I know we've been working directly with the Hologic folks but I don't know if--

DR. CRAWFORD: Well they didn't do a stellar job so--

MR. BAKER: Well they were never in urology.

DR. CRAWFORD: I know.

MR. BAKER: They acquired a product--

DR. CRAWFORD: They got Gen-Probe and they inherited it and they just sort of let PCA3 sort of slide away. Right Scott?

M. SCOTT LUCIA, MD: Yeah.

DR. CRAWFORD: I mean what are your feelings?

DR. LUCIA: And that's what happened with the reimbursement landscape.

DR. CRAWFORD: We got a lot of good data on PCA3, that this is not, I mean Hopkins got data, lots of people have data on PCA3. You have data.

MR. BAKER: Yeah.

DR. CRAWFORD: And it's just been circling the toilet and nobody can flush it.

DR. FINKELSTEIN: I'll tell you what happened to us. We were heavy PCA3 users and then Bostwick took it over, and Bostwick started running the assay and then they came around and said you know what? You don't have to do the rectal exam and a lot of people stopped, in my department stopped doing the rectal exam because the Bostwick rep said you don't have to do the rectal exam. And we got such nilly-willy results, nobody ever recovered from the don't

do the rectal exam Bostwick spiel that we got a few years ago.

DR. CRAWFORD: Why would they ever say, people, that was a misconception. I mean you ask - - about it. you don't need to do a prostate massage you need to do what it called an attentive--

DR. FINKELSTEIN: An attentive, right, no.

DR. CRAWFORD: You just go like that. You don't have to--

DR. FINKELSTEIN: Bostwick was promoting that his assay worked just was well without the rest of the rectal exam.

MALE VOICE: Where in the hell did he get that?

DR. FINKELSTEIN: I'm just saying because that's where we sent all of our PCA3s two or three years ago.

DR. CRAWFORD: Yeah he was into, he was into that. He's been into PTEN/ERG and everything else he was doing. Brawer, what do you - - ?

MICHAEL BRAWER, MD: Back to ProMark if we can. Do you have any, I mean your validation study you would know who failed radical but in the paper you don't show any real oncologic endpoints. Are you guys going to, do you know that data or are you going to show that?

MR. BAKER: In terms of, in terms of who failed?

DR. BRAWER: Yeah.

MR. BAKER: They were all confirmed on radical. I'm not sure I understand the question.

DR. BRAWER: Well but it's more important other than yeah they're confirmed that they were upgraded or upstaged--

MR. BAKER: Right.

DR. BRAWER: But you didn't show whether it predicted who failed the treatment. Right? There's no data in the paper about that. I just wonder why.

MR. BAKER: Well that, yeah that wasn't within the realms of that particular validation study. That's been a question that's been raised before for follow-on research.

DR. CRAWFORD: Okay, that's good enough. One quick follow on. In the paper it sounds like, I mean I'm not sure I understand it but is that do you not, can you not give an answer in 61% of the patients tested? In other words you give a prediction for the low and you give a prediction for the high.

MR. BAKER: Sure.

DR. CRAWFORD: But two thirds. How can, I don't see, it's a continuous output. Right?

MR. BAKER: Sure. So excellent question because I think again our forerunners in this space have challenges with producing a robust response to these patients that you have the most difficult managing. I think what's important to understand with ProMark is that we have not only in our studies but in our post marketing research collected data that provides actionable results in four out of five cases. Now if anybody comes and tells you that they've got 100% marker in this space I mean they're crazy. But this is a space for a few years go. You had nothing like this in this space. So we have intermediate scores in the 50 to 65 range that you will still find yourself on the fence saying hey I was there before the test, I'm still on the fence now. It provides you just initial information that, or additional information that you're still there and you've got to probably go back to the histology and the other clinical work, and quality of life and active sex life and so forth to determine whether to stay on watchful or active surveillance or take them to treatment. But we clearly, we do have that data on file. The validation study, you're correct though, the validation study on the extremes above 90 and below a score of 33 have very high specificity and that represents the extreme ends of the study. But a patient, I would argue that a patient with a score, a ProMark score of 80 is a fairly strong argument for treatment and a patient with a score of 40 is below the national average of 27% of the patients that progressed to aggressive disease. So another good argument for again going back to your clinical work again the value with ProMark is you get the score back and you can pull the entire workup back together again and illuminate your decision, where with the other markers you're kind of at an endpoint at that point because you've included all of that information in their prognostic report.

DR. CONCEPCION: Hey Kevin, I mean I think everybody, every biomolecular company has challenges whether it's Myriad or whether it's MDX Health, whether it's Genomic Health. So your proteomic test you use IHC in order to run your assay. Correct?

MR. BAKER: Yes.

DR. CONCEPCION: My understanding about the test is there are some, there are some limitations on when this test can be used in relation to how the tissue was actually processed.

MR. BAKER: Correct.

DR. CONCEPCION: And how, and given the fact that I bet if I asked 50 urologists if they knew exactly how their biopsies or tissues were processed from the time we pull it out from the needle. How do you, how are you going to overcome the fact that you cannot use some tissue staining in the processing of the specimens that ultimately may result in a change of how urology practices actually perform?

MR. BAKER: Sure. It's more of a pathology question but there's certainly--

DR. CONCEPCION: No, it's, I mean for big urology groups it's a urology question because we have our own pathology labs.

MR. BAKER: Right, right, and we're talking specifically about eosin, which is a marking stain that does interfere with the running of the test. We do have and provide stain workarounds, substitutes that we provide for either - - , community practices, community pathology, and academics, and they're very simple staining solutions that don't interfere with the ProMark testing. But that is the most significant interference. Now--

DR. PETRYLAK: Have you looked at rapid fixes?

MR. BAKER: I'm sorry?

DR. PETRYLAK: Have you looked at rapid fixation protocols, rapid processing protocols?

MR. BAKER: I don't believe we've looked at those yet.

DR. PETRYLAK: So those are notorious. So we evaluate a rapid processing protocol. It sounds like a great idea. Right? You can have your results back in six hours. The problem

is the rapid processing protocols destroy a lot of tissue antigens and we've found very specific deletions of antigens when we use rapid processing protocols, and those are very popular in community-based settings.

DR. CONCEPCION: When you say rapid like microwave and--

DR. PETRYLAK: No, it's actually within a processor that does rapid processing.

MALE VOICE: Right.

DR. PETRYLAK: And what we've found was, what we think is going on is inadequate fixation at the time it's heated. So it uses a heat treatment step rather than a room temperature step, and the heat actually damages the isotopes. And we saw some very specific things that went on, particularly in the transplant setting and that's in the setting that you really want rapid turnaround to evaluate rejection. Well it was knocking off key epitopes that we look at when evaluating transplants. So I think these things need to be looked at when looking at protein markers.

MALE VOICE: Yeah.

DR. PETRYLAK: Make sure that you're not losing epitopes just because of how the tissue is handled.

MR. BAKER: We're starting to evaluate microwave specimens because we're not sure whether microwave interferes with it. But back to the eosin, I mean the important clarification on that is that is a marker for location. It has no clinical value other than to be able to find the specimen when the histo techs are moving the tissue. And that's why we provide the simple solutions for that and we, you know, it's not disruptive. We are able to do that on a large-scale laboratory or small-scale laboratories. The ideal thing is not to add the ink actually into the processor at all but if you do we've got the substitute inks for that.

DR. CRAWFORD: All right, we've got to move. Okay, Wim.

WIM VAN CRIEKINGE, PHD: Maybe I got it wrong but did you say you were going to give some insight in the algorithm behind using the eight HIC markers and how they are combined or not combined?

MR. BAKER: I couldn't speak to the algorithm. We've got it on file. I'm happy to get it to you. It is one of the more popular college-based algorithms that's used in this type of industry. But it's important that these markers are not additive, they're multiplicative. The algorithm is one, you know, you don't add the value of each marker. Each one by itself is robust and aggressive in assessing aggressive risk of cancer, but combining them doesn't have an additive result, it has a much more powerful result. I couldn't really speak beyond that in terms of the specific algorithm but we do have that data available.

DR. CRAWFORD: All right, thank you. Marc?

MR. BAKER: Thanks very much.

[Applause]

Session 5: Genitourinary Cancer Research and Healthcare Coverage – Marc B. Garnick, MD

Featured Lecture: Healthcare Coverage and Reimbursement – Marc B. Garnick, MD

DR. GARNICK: - - brief talk.

DR. CRAWFORD: Huh?

DR. GARNICK: You know I'm giving a talk instead of the person that didn't show up.

DR. CRAWFORD: I didn't know that.

DR. GARNICK: Okay so the--

DR. CRAWFORD: I have to okay that by the CME people.

DR. GARNICK: - - this other guy. So Dr. Jeter was unable to come. Dave, did you know that?

DR. CRAWFORD: No, I did. She had some federal court thing she had to go to.

DR. GARNICK: Okay and her talk was healthcare coverage and reimbursement.

DR. CRAWFORD: Okay.

DR. GARNICK: And I thought what I would do is to just go through some screening issues and then delve into issues relating to healthcare. I feel particularly appropriate to do this for two reasons, number one for the last ten years I've been involved in the screening program of the American College of Physicians which has looked at prostate cancer screening with an either great debate format or a pro and con, and the first time they did that was Dr. Cataloni [phonetic]gave the pro on PSA-based screening and I gave the con, and sort of a morphed into a screening discussion on prostate, breast, and lung cancer, and I'm going to go through some of the issues relating to that. And then as it relates to health reimbursement Dr. Schnipper who's our division chief of the Beth Israel Deaconess Medical Center has been the chairperson of the ASCO committee on looking at value of cancer treatment options as well as designing the ASCO five key opportunities to improve care and reduce cost, and I'm going to go through those with you as well to initiate some discussion relating to those.

I actually see this meeting really as a tipping point for the leadership of the American Urological Association to really change the way the guidelines are being done and incorporate biomarkers into decision making earlier on. And I think that the discussion needs to be directed a little bit differently in the fact that what I've heard for the last day or two has been this biomarker is going to tell you to treat, this biomarker is going to tell you to biopsy. Those are all fine and wonderful events but they should be utilized to design studies to then test whether the treatments that are being directed as a result of those biomarkers are actually effective. So I just want to make a few comments. Everybody's been throwing out darts at the United States Preventative Services Taskforce on screening guidelines but I'm also going to go through the American Urological Association guidelines, the American College of Physicians, and the Canadian Taskforce on preventative healthcare for prostate cancer screening. I'm then going to delve very briefly into some breast cancer screening metrics, which have very, very provocative information associated with them.

Okay so the ACP basically, have recently revised their guidelines that in men between the ages of 50 and 69 to inform of the potential benefits and significant harms of

PSA testing. No testing for those who do not express a clear preference for screening, no PSA testing for less than 50 or over 69, or a life expectancy of less than 10 to 15 years. So those are the most recently revised guidelines from the American College of Physicians, and they have a wide spectrum of talking points.

The American Urological Association, which really actually initially fought the Preventative Services Taskforce recommendations have come up with these guidelines just recently published within the last 12 to 14 months. No PSA testing for those men under the age of 40. PSA is not recommended for those between the ages of 40 and 54. If you are 55 to 69 to prevent mortality and 1 in 1,000 men over ten years PSA testing should undergo a shared decision making based upon values and preferences. So their most positive information for recommending screening is that it prevents mortality in 1 of 1,000 men screened and detected over ten years, and they recommend the shared decision making. For those screened they recommend every two years, and no PSA testing for men greater than 70 with less than 10 to 15 years of life expectancy.

So this is a very, very different recommendation that had been done after the task force had come out, and I believe they were under intense pressure basically to have rejected all of the evidence-based information on screening guidelines. And to me I'm not sure these screening guidelines make any more sense than the others but it would seem to me that incorporated into PSA screening have got to be discussions about PSA biomarkers and prostate cancer biomarkers to inform the appropriate decisions.

The Canadians I think really have it right, and I think this is from Dr. Gomella's journal that was just recently published. Between men under the age of 50 and greater than 70 there's a strong recommendation against screening and they go as far as saying clinicians should not routinely discuss screening unless the topic is raised by the patient. So these are the Canadian guidelines. For men between the ages of 55 and 69 there's a weak recommendation against screening once you discuss the risks and benefits, and for those who place a high value on a small potential reduction in mortality and are less concerned with undesirable consequences may choose to be screened.

So even though the taskforces come out with basically saying no PSA-based screening should be recommended your urological organizations have come out with similar but not as strong recommendations. And so I guess there's some unanimity of opinion relating to that. And again, I think these can be more precisely defined with the use of biomarkers to help inform decisions.

Okay, so I just want to make a few comments about breast cancer as well because everyone says there are many similarities between breast cancer and prostate cancer. And so I just want to go through the issues of mammography. I'm not sure if the people in this audience follow the breast cancer controversies on screening mammography but there are now three large randomized prospectively evaluated studies on a lot of older information. There's an Oxford University study, there's an Ottawa study, and there's just a recent study from the SEER database in JAMA looking at over 16 million women. And not one single of those large studies following the introduction of widespread screening mammography have shown an improvement in survival based upon screening mammography for women from breast cancer.

And this is a paper you may or may not have seen. It was published in the New England Journal about a year ago, and it was entitled, "Abolishing Mammography Screening Programs: A View from the Swiss Medical Board". And so the Swiss government basically identified a group of individuals to take a look at all of the information relating to screening mammography and the potential benefits. And this is an absolutely fascinating paper, and the citation is there, and I would urge you to take a look at it and really understand what the implications of this paper are.

So this is a graph from the paper, and this is on Panel A it's the women's perception on the effect of mammography. And this is 1,000 women at the age of 50 who would undergo screening mammography on an annual basis. So women's perception that with screening over a period of ten years 80 women would die from breast cancer, while in fact without screening they felt that 160 women would die without screening mammography, while in fact shown on Panel B the actual number of women who would actually die from breast cancer with screening is four and without screening

it's five. So it's very, very similar to 1,000 men with prostate, undergoing screening for prostate cancer that would actually save their life, 1,000 men screened over ten years would save one life. It's virtually identical information to the women's screening mammography information.

And the authors go on to state that it's easy to promote mammography screening if a majority of women believe that it prevents or reduces the risk of getting breast cancer and saves many lives through early detection of aggressive tumors. We would be in favor of mammography screening if these beliefs were valid, unfortunately they are not, and we believe that women need to be told so.

From an ethical perspective a public health program that does not clearly produce more benefits than harms is hard to justify. Providing clear, unbiased information, promoting appropriate care, and preventing over diagnosis and over treatment would be a better choice. So I leave that, I leave that information with the following metric, which is almost identical to what would happen for prostate cancer. So here's a balance sheet of screening mammography in a 50-year-old woman undergoing 1,000 women 50 years or older undergoing annual mammography for ten years. One woman would avoid breast cancer death. Okay? The harms would be that between 2 and 10 would be over diagnosed and treated needlessly, between 5 and 15 would be told that they have breast cancer earlier than otherwise yet have no affect on their prognosis, and between 200 and 500 women will have at least one false alarm, and 50 to 200 will be biopsied. So this is sort of the circumstance that is very, very difficult to digest but as I said the three largest studies that have looked at overall mortality in Oxford, in Ottawa, and the SEER database have not shown any improvement in survival despite the widespread utility of screening mammography.

Okay so why am I even talking about this? I'm talking about this in terms of a talk that I was asked to give about an hour ago to fill in for Elaine Jeter on healthcare issues, and I think you should be aware that the American Society of Clinical Oncology, which is the governing organization that Dan and I belong to from a medical oncology--

DR. CRAWFORD: I belong to it too.

DR. GARNICK: And David belongs to.

DR. CRAWFORD: And some other people in here.

DR. GARNICK: Okay, is really the governing cancer organization. They have come out with so-called opportunities to improve care and reduce costs. The top five list for oncology, and one of them has to do with prostate cancer, and I just want to go through them because I think you should be aware of them. The first one is don't use cancer-directed therapy for solid tumor patients with the following characteristics; low performance status, i.e., a performance status of 3 or 4, no benefit from evidence-based interventions, not eligible for a clinical trial, and no strong evidence supporting the clinical value of further anti-cancer treatment. And this is based upon the fact that a substantial proportion of the healthcare budget goes into the management of patients basically in their last four to six weeks of life. And I'm really listing these for discussion after my presentation.

The second one is don't perform PET-CT or radionuclide bone scans in the staging of early prostate cancer at low risk for metastases. Okay so that's a guideline.

DR. CRAWFORD: That's been an AUA guideline for a long time.

DR. GARNICK: Yeah, so that's very, very important. I could see how a biomarker could potentially influence that recommendation. Okay. Don't perform PET-CT or radionuclide bone scans in the staging of early breast cancer at low risk for metastases. So a virtually identical situation to prostate cancer.

Don't perform surveillance testing of biomarkers or imaging for asymptomatic individuals who have been treated for breast cancer with curative intent. Okay, so that's sort of almost a parallel for prostate cancer except we do have PSA as a better indicator. And don't use white blood cell stimulating factors for primary prevention of febrile neutropenia for patients with less than a 20% risk of this complication. And ask Dan, would that apply to docetaxel or not? Would that apply to docetaxel?

DR. PETRYLAK: - - .

DR. GARNICK: I'm sorry, don't use colony stimulating factors for primary prevention of febrile neutropenia for patients who have less than a 20% risk of this complication.

DR. PETRYLAK: Technically it would because it's about 5%.

DR. GARNICK: Okay.

DR. PETRYLAK: With docetaxel. But again you've got to look at your patient as well.

DR. GARNICK: Okay so those are the five things from ASCO relating to quality improvements, and I think the other thing you should be aware of is there's been a lot of press recently really initiated by Dr. Schnipper at our institution on looking at the issue of financial toxicity that patients with cancer face. And basically like other toxicities of cancer treatment financial toxicity resulting from out-of-pocket treatment expenses can reduce quality of life and impede delivery of high quality care. Patients experiencing high out-of-pocket costs have reported reducing their spending on food and clothing, reducing the frequency with which they take prescribed medications, avoiding recommended procedures, and skipping physician appointments to save money. These unintended consequences risk an increase in health disparities which runs counter to some of the key goals of healthcare reform. And so those are the comments that I wanted to make and I'd like to open this up to discussion to see what--

DR. CRAWFORD: It sounds like something from a presidential debate from Massachusetts and the leftist approach here. And it's not balanced because there's not the other side. But go ahead anyway.

DR. GARNICK: I mean this is like arguing with motherhood and apple pie David. What the ASCO taskforce is basically saying--

DR. CRAWFORD: Yeah but they'll go out and buy a God damn big TV and everything else, you know? And have a nice car. You have to spend some money on healthcare. I mean come on.

DR. GARNICK: No, this is the out-of-pocket cost for the patient.

DR. CRAWFORD: So what's wrong with an out-of-pocket cost?

DR. GARNICK: Well not--

DR. CRAWFORD: Are we giving free healthcare to everybody? Maybe Massachusetts does but I don't know that Colorado does.

DR. GARNICK: No, so when we're trying to make a determination of selecting Zytiga or abiraterone or enzalutamide versus ketoconazole we go to the patient and we say you're out of your, your monthly copay can be as high as 2,500 dollars.

DR. CRAWFORD: Yeah, and then the people who are on fifth-line therapy for non-small cell lung cancer it gives them a one-day benefit and it's on a plenary session of ASCO. Come on. I mean--

DR. GARNICK: Dave, we're saying the same thing.

DR. CRAWFORD: No we're not.

DR. GARNICK: Yes we are. We're saying that that shouldn't be done. And the whole purpose of the value of cancer treatment options is to discuss the financial implications of their therapy and basically include that as part of the conversation and having the patient understand why the most expensive spread is not necessarily being applied to them.

DR. CRAWFORD: Well that's not what you said. You were talking about out-of-pocket expenses. I have out-of-pocket expense it burns me because I'm taking statins and other things that aren't covered by insurance company because they say we're only going to pay for the generic stuff which I tried and didn't work. And they still, so I'm paying hundreds of dollars a month out of my pocket. It hurts but I do it.

DR. GARNICK: But those statins are probably life extending and they're probably having important medical benefits. But what I think this--

DR. CRAWFORD: I eat more at Subway than I do at other places because I can't afford to go out to eat like, you know.

DR. GARNICK: I would like other people to discuss with--

DR. CRAWFORD: All right Marc. Okay.

DR. PETRYLAK: Yeah, I think one point that I've become very distressed about is this issue about end of life care and all of this money being spent at the end of life. And

there has been a push at my institution that we should be pushing patients more towards having palliative care involved at the end. I think that is totally misguided, and from a standpoint that it's more ticking off the checklist as to what Medicare wants to see and what the government wants to see. I can accomplish just as much in taking care of a patient at the end of their life if I've got a good nurse practitioner and not have the patient be transferred over to a palliative care doctor who then does not know the patient, does not know the family, and the patient goes to the sense of feeling as if they are being abandoned. And I think that this whole issue about the last couple of months is very, very misguided. It is being looked at as a check off the box type of situation and not necessarily being used as a way of delivering the best care to the patient and the most compassionate care to the patient at the end of life.

DR. CRAWFORD: Okay.

DR. PETRYLAK: And one last point. We've also gotten a lot of flack recently about using chemotherapy in the last month, and I think that that also should be taken in the context of a lot of these new drugs that we're using do in some situations have a Lazarus effect, and I think that by perpetuating this type of attitude, not engendering discussions between physicians and patients but making more rules I think the patients are losing out for it.

MALE VOICE: [Off mic] - - .

DR. CRAWFORD: There's a comment here.

FEMALE VOICE: Well, I was just going to say I talk with a lot of patients who, as a matter of fact we just lost one who it was important to him to live longer and he never got the opportunity to have that discussion about quality of life, palliative care and all of that. So I think that there's, we have to, I mean cost is important and we all agree with that but so is what a patient wants. And somehow what the patient wants and his longevity is being kind of pushed to the side more and more recently, and we see that more and more in our nonprofit group.

DR. PETRYLAK: I think we're saying the same thing I think but what I don't like is this attitude of credentialism that again says that a palliative care person is anointed, they

all of a sudden charge in and, you know, I had a palliative care doctor say that your doctor is no longer involved in your care.

DR. CRAWFORD: Said what?

DR. PETRYLAK: I had a palliative care physician walk into a patient's room after I had the long discussion with the patient about hospice and the fact that we were going to send this patient to a hospice, and I said I'm always your doctor, you're not losing me, I'm here to answer questions and help the other doctors out. The palliative care person comes in after that and says he's no longer involved in your case, I am.

DR. CRAWFORD: Wow.

DR. PETRYLAK: But we're seeing a lot of this.

DR. CRAWFORD: That's what's happening and when somebody goes to the intensive care unit they don't belong to you anymore.

DR. PETRYLAK: That's, that's, but you're still following that patient along with the intensive therapy.

DR. CRAWFORD: Yeah, go in there and try to say something and see what happens.

DR. PETRYLAK: Okay.

DR. CRAWFORD: No, Dan I agree with you.

DR. PETRYLAK: Yeah.

DR. CRAWFORD: And this is just how we're driving up the cost of medicine and everything else. Cliff?

DR. VESTAL: I agree with everybody.

DR. CRAWFORD: You shoot them down in Texas, right? You don't--

DR. VESTAL: If they're still alive when they get there. They've already been shot usually.

DR. CRAWFORD: Yeah.

DR. VESTAL: But I agree with you Dan. It's very disconcerting because what we in urologic oncology preaches that they're your patients until the very end. You take care of them, you know them better than anybody else in urology, you guys

in oncology have taken care of these guys for a long, long time and they do not, the patients and the family know you best and they expect you to give them good advice. And that advice is you know it's time to quit, it's time to do this, it's time to do something else. But what you're seeing is that the chemistry of a family's life is being interrupted by putting these strangers into their most precious time, which is the end of life. But what I see is that the same thing going on with your medications. You can use the generic like Crawford said, it must be his end of life because they're only giving him generics. But the fact is they're telling you want you can use and not use on the medical side. Now they're going to tell you what you can and cannot do on the social side. It's just a squeezing of your rights as a physician to interact with that patient in both the scientific and in the social aspect of what you do as a living, and I find it appalling that someone can tell me that I'm no longer that person's physician.

DR. CRAWFORD: So then how is pain managed at Yale? I mean who manages the pain at the terminal stages?

DR. PETRYLAK: The palliative care team does come in at this point, and I've had disagreements with them as far as the pain management goes. I mean I've had 22 years of experience in pain management. I've had people who maybe are not as experienced in doing so. So I think that it's again you've got to have cooperation between physicians and there's got to be a quid pro quo. But the important thing is the patient's best interest being managed. And I mean for example the nurses are right to call a palliative care consult, even though as the attending physician I may not request that. And again, this is being mandated by this whole issue about what the cost is in the last month of somebody dying. In fact, I think hospitals are now being looked at in terms of whether somebody dies in the hospital or not or whether they actually make it to hospice. And that may have influence on their scores and their reimbursement patterns.

DR. CRAWFORD: Yeah.

DR. PETRYLAK: Which I think is ridiculous.

DR. CRAWFORD: Okay. Let me, there's actually some questions

that came through Marc. PSA screening, surely the issue is not whether to do the test, it should be what to do with the result. Just having the PSA value is only one piece of information to be added to age, race, family history, when deciding whether to do anything or nothing. So this is the separation of diagnosis from treatment. This isn't even diagnosis, it's a bit of information that you might act on.

MALE VOICE: But David?

DR. CRAWFORD: Yeah?

MALE VOICE: Well I don't know why you didn't mention the EAU guidelines who clearly say what David was just saying. They advise with level 2B in the guidelines that an initial PSA in all men over the age of 50 and absolutely in men at least for prostate cancer because of the family history and so on. And you didn't mention that just one value of PSA at the age of 50 is starting to make a decision whether to repeat the PSA every year, every two years, or every ten years. You did not mention that.

DR. GARNICK: I'm sorry Frans [phonetic]. The guideline is what? PSA testing in men over the age of 50?

MALE VOICE: Well PSA, initial PSA base value for every man. That's what the EAU guidelines say.

DR. GARNICK: And then how often after that?

MALE VOICE: Well it depends on the results that you see. If you have for example a value of less than 1.5 as we discussed yesterday you can leave the patient for five years and up to eight years.

MALE VOICE: Yeah.

MALE VOICE: And the European study says if the PSA is lower than 1 you just have to forget about repeating PSA and do it every eight years or every ten years.

DR. CRAWFORD: That's sort of Hans Lilja's work and Vickers and that, and they just came out, Thompson came out with PSAs of less than 1 come back in ten years, and it sort of goes along with what I was talking about yesterday. But yeah regarding the EAU guidelines I agree with you. They are much better than anything we have in the U.S., plus their patient education stuff is friggin' amazing. And you know

most American urologists don't look at their website. The educational material they have for patients just runs circles around what we do.

All right Marc, so one more question. Regarding all of the combinations of screening data collections how can noise and confounding factors possibly be removed to draw good conclusions? So is there a way forward I guess is what that's saying.

DR. GARNICK: Yeah, I think there's a way forward.

DR. CRAWFORD: Okay.

DR. GARNICK: And to me the way forward is to incorporate a PSA test basically and then use some biomarkers as the way forward. I mean you've got to incorporate biomarkers into treatment algorithms to see if the treatment they were recommending based upon the biomarkers is effective.

I don't see any--

DR. CRAWFORD: I don't understand, I'm not sure I understand what you're saying.

DR. GARNICK: Yeah, okay. What I'm saying is I don't see any, if we're having this meeting ten years from now, okay? You may have biomarkers that say yes this patient should have a biopsy, this patient should be treated. But that begs the question of whether or not the treatment is being offered as a result of the biomarker is effective or not.

DR. CRAWFORD: What's the definition of effective then?

DR. GARNICK: A randomized study that takes a population of patients with prostate cancer with a specific biomarker in which treatment versus observation or treatment A versus treatment B is basically conducted.

DR. CRAWFORD: Do you think that's going to happen?

DR. GARNICK: No it's not.

DR. CRAWFORD: Okay. I don't either.

DR. GARNICK: But that's the only way we're going to get out of the conundrum.

DR. CRAWFORD: Well, we still don't have a study of radical versus radiation and we still don't have good studies of

screening, and it's a mess.

DR. GARNICK: But what I'm saying is that in the two large screening populations there have got to have been equal numbers of patients with adverse features that in the screened population got treated and in the unscreened population either did not get treated or got treated very, very late in their disease. And if the treatment was effective in the screened population we should have seen overall survival differences between the screened and treated versus the unscreened.

DR. CRAWFORD: The most contemporary one that showed that was PIVOT, that showed that people that had more locally advanced/advanced disease actually did benefit from treatment.

DR. GARNICK: There's no question about that. That was a small subset analysis. As a matter of fact the low-risk patients in PIVOT actually who were treated with radical prostatectomy--

DR. CRAWFORD: I know.

DR. GARNICK: --had a shorter survival compared to the observation patients. So to me the intrinsic question that has not been asked and has not been answered is whether or not treatment for patients with high-risk features is effective in prolonging survival.

DR. CRAWFORD: I don't know what high-risk features are but--

DR. GARNICK: Well those would be, you know, those would be--

DR. CRAWFORD: I mean I don't know what they are.

DR. GARNICK: Well patients that would have a short progression-free survival and overall survival based upon current studies. Gleason 8, 9, and 10 cancers, patients with T3 disease, patients who have a rapid time to biochemical relapse, rapid time to metastatic disease. All of the stuff that Friedlander [phonetic] looked, from the original Pound data. Those are high-risk patients. Those patients die of prostate cancer. And when those patients are clinically localized and present whether from screening or from digital examination does our treatment affect any effectiveness in improving survival? And that question to me has not been answered.

DR. CRAWFORD: Well you're not making a good argument because the Pound data were people that were treated at Hopkins by radical prostatectomy, so it's not going to answer that and it's going to talk about people that had biochemical failure. We need a randomized trial verily versus delayed and all of that, and that's never happened. I mean it's never been accomplished.

DR. GARNICK: But those patients would have been included in screening studies is my point.

DR. CRAWFORD: Yeah well and again the issue was PLCO. People weren't told to be, they had to be biopsied, they weren't told how to be treated because it was what happened in the community and so that's, and from that standpoint it's what happens in the community. It was a valuable trial. And what screwed the whole thing up to a degree was the fact that screening sort of, it was a day late and a dollar late to start the study. It was supposed to start five or six years before. It didn't because of all of the delays by our congresswoman in Denver, and adding all of the other, all the other sites like lung and ovarian and colorectal that by the time it got started a lot of people already had a PSA.

DR. GARNICK: But Dave let me, so if you were advising President Obama.

DR. CRAWFORD: That would never happen but anyway.

DR. GARNICK: Or Ronald Reagan. Okay? What would you advise him or her to do in terms of trying to answer this question? If all of the governmental resources were available to you what would you do?

DR. CRAWFORD: What's the question?

DR. GARNICK: The question is what should we do for the screening of the common cancers, breast, colorectal, lung, and prostate? Let's talk on prostate.

DR. CRAWFORD: Well first of all we found, first off we found out that ovarian didn't work and we actually killed more people than we screened.

DR. GARNICK: Correct, okay.

DR. CRAWFORD: Okay? There's nothing, there's nothing new

there. Okay? Lung cancer actually with CT, spiral CT scans we actually did save some lives but we also subjected a lot of people to thoractomies and this and things that didn't need it. Okay? So that's, okay colorectal I think that's solved I mean to a degree. Now there's new tests out. What's the test you guys got? Chris? What's the colorectal screening thing you guys have?

CHRISTOPHER THIBODEAU: Oh, we out license our gene technology to Exact Sciences. It's the Cologuard assay, the stool-based assay.

DR. CRAWFORD: So you have a test that screens for colorectal cancer that works. Okay? So now let's go back to prostate. What happened to prostate? What happened to prostate is the pendulum swung too far, not separating diagnosis from treatment. Right?

DR. GARNICK: Yeah, absolutely.

DR. CRAWFORD: And we had a bunch of greedy people, you know, IMRT and protons and neutrons and everything else that we were treating a lot of people that didn't need to be treated and I think we knew it.

DR. GARNICK: And you bought a - - .

DR. CRAWFORD: And then we had surgeons who got robots and then surgeons that wanted to add numbers to the number of cases they were doing. That all, that all happened, and then we scared the shit out of people that had Gleason 6 cancers. We can't tell you that you don't have a Gleason 8. And that's true because 30% of the time you did, and so we would operate on two-thirds for that one-third. So that's where genomic markers would have made a difference and we have, we have them now. So I would say that we need, you're right in the way the markers can help us we've got to go forward and we have to do the actionability part of them. they've already done the other stuff. We have to do the actionability part, that if you do it and you follow it we're going to be good citizens again. I don't think we have to go back and reinvent things. I think screening for prostate cancer works in the right person and it doesn't have to be somebody that you're defining that's 8, 9, and 10, and more advanced that's where, that's where the medical oncologists need to come in with all of these, you know, whatever new drugs to do it. We don't want to find

those people. We want to avert that from happening.

DR. GARNICK: But I mean ten years from now when you're 50 years old and I'm maybe 52 are we going to have made any progress? Unless we change the paradigm I don't see we're going to make any progress.

DR. CRAWFORD: Well that's what I'm saying, we have to change the paradigm. We have to say, we have to do what I said yesterday in that little talk. I mean I think we've got to, we've got to, we've got to make it simple, we've got to act on stuff, and we've got to stop finding cancers that don't need to be treated, we've got to cut down on the biopsies, but we got to find ones that probably benefit.

BRIAN MORAN, MD: Dave, look at historically though. I mean PSA made an impact since late 80s dropping the mortality rate in this disease and so is the answer going to lie in looking at mortality rates five years down the road? Because we are seeing more advanced cancers in our clinic. I mean definitely.

DR. CRAWFORD: Well the argument about the mortality rate, because I can argue screening pro or con either way because I do it all the time. The thing about mortality rate is that other things have changed in the way we take care of people, statins and people are living longer and all of these other sorts of things, and so yeah they live, and then it's a lead-time bias and everything else that comes into play. So do I believe it? Yeah I believe it but you can argue it the other way effectively if you want. And yet get people that like Vickers and some of the others that are out there pretty controlling and they tend to win those sorts of arguments. But I don't know. You and I both believe that it helps some people, but you and I both know that we have over treated a lot of people.

DR. MORAN: Definitely.

DR. CRAWFORD: A urologist comes to you and he's got somebody with Gleason's 6 and two cores 5% and Brian we want to put seeds in this guy. You're not going to tell him no. Come on. You haven't. You might now but you never used to.

DR. MORAN: I'm going to tell them focal therapy should be considered. I mean--

DR. CRAWFORD: Yeah, but you're still, I mean okay.

DR. GARNICK: We need a urine-based test that could identify patients that need a biopsy, do the genomics on that biopsy, and then do randomized studies with treatment versus A, B, or C.

DR. CRAWFORD: Okay and what are we going to do in the interim?

DR. GARNICK: That's--

DR. CRAWFORD: Let people die?

DR. GARNICK: Right now, well--

DR. CRAWFORD: Marc, do you think, do you think it's possible that we will ever do another in the U.S. a randomized trial for early-stage prostate cancer?

DR. GARNICK: I don't think, it would take another 25 years.

DR. CRAWFORD: No, I mean no one would do that.

DR. GARNICK: Yeah.

DR. CRAWFORD: I mean the PIVOT was the last and it's, you know--

DR. GARNICK: It's sad.

DR. CRAWFORD: It will never happen but you can approximate. Some of it, like your high-risk study might be able, if someone would believe biochemical recurrence is a surrogate of badness, not definitive but it's--

DR. GARNICK: Enriches the pool who's going to fail.

DR. CRAWFORD: You probably could do a localized high-risk study with the markers. You know? With a five to ten-year horizon. You probably could get an endpoint there.

DR. GARNICK: You could.

DR. CRAWFORD: But you're never going to get a mortality like we had in PIVOT. It's just not going to happen.

DR. GARNICK: No, what I'm saying is but if we had some methodology of identifying those patients that were destined to become a biochemical relapser and before their local therapy.

DR. CRAWFORD: But to your point you've got to randomize and half get the biomarker and half don't.

DR. GARNICK: Yeah.

DR. CRAWFORD: Otherwise you don't know the answer.

DR. GARNICK: Well everyone gets the biomarker and half get treated and half don't.

DR. CRAWFORD: Yeah, there's got to be a randomization. What happened to your slides?

Clinical Trials Discussion Panel – Marc B. Garnick, MD, Daniel P. Petrylak, MD, Karl J. Kreder, MD, MBA

DR. GARNICK: Okay I don't know--

DR. CRAWFORD: You're not done, you weren't done are you?

DR. GARNICK: I was done. I'm just the moderator. The next thing is the clinical trials discussion panel.

DR. CRAWFORD: And you're the moderator of that too. That's what we're doing right now. Okay.

DR. GARNICK: Yeah, that's exactly what we're doing.

DR. CRAWFORD: Okay. Will Dan Petrylak, Karl Kreder, Elaine Jeter, and Marc Garnick please start talking. So I guess that would be, the future would be what you just said. I mean we've been beating you down but you're going before, I had the opportunity to go before the U.S. Senate a number of years ago and be grilled and questioned by Senator Shelby and his committee on why Medicare should pay for PSA. And you know what? We won. And so McCloud [phonetic] and I were pivotal in getting that started. All right, so do I feel bad about that? No. So now a year before the, Senator Shelby is still around, before his committee what would you tell him we need to do to go forward.

DR. GARNICK: I don't think, I mean we have to start from square one basically, that's where we have to start. And if you take a look at the time that's allowed us from PIVOT, actually from PLCO and from the European randomized study we are no further along now than we were when those studies

started, and we're not going to be any further along in another 15 years unless there's a significant paradigm shift in how we're looking at these questions, especially with a lack of any definitive evidence-based information that anything we do for localized prostate cancer is beneficial except for preventing local complications. And I don't see how we're going to--

DR. CRAWFORD: Okay so what's the way to go forward? Okay but you can't just stop dead and close your eyes, you know, see no evil, hear no evil, speak no evil that prostate cancer screening is going to stop, that all the treatments are going to stop, people aren't going to die. So you have to do things in tandem.

DR. GARNICK: Okay.

DR. CRAWFORD: So something's got to go forward and then something needs to built on it in the way of the study.

DR. GARNICK: So I think biomarker evaluation of newly diagnosed localized prostate cancer is absolutely the key for helping design subsequent studies. Okay? If you've got a Gleason 3+3 cancer and you've got none of the adverse biomarkers that patient should be left alone or continue on extra surveillance. If you've got adverse biomarkers those patients should be randomized into studies whether it be surgery versus observation, radiation versus observation, early hormonal therapy, early chemotherapy. We've got to do something differently to show that the impact of our treatments are actually affecting improvements in overall survival and basically improving quality of life. Otherwise we're going to be in the same conundrum in which every specialty, whether it be brachytherapists, robotic surgeons, radiation therapists, or radiation oncologists, medical oncologists, are going to have their own pigeonholed area of enlightened self interest.

DR. CRAWFORD: Yeah but okay that's great, that sounds like a politician that you said that but it didn't mean, nothing's going to happen. So how do you, what is the concrete thing to do?

DR. GARNICK: The fact that PIVOT was able to be conducted was amazing.

DR. CRAWFORD: Yeah but--

DR. GARNICK: Diagnose patients with prostate cancer--

DR. CRAWFORD: Everybody shoots PIVOT down.

DR. GARNICK: I think PIVOT was an incredibly important study.

DR. CRAWFORD: Well we were part of PIVOT too. Brawer was the co-PI.

DR. GARNICK: I know.

DR. CRAWFORD: Why is it--

DR. BRAWER: And it took, I always, my favorite slides though are the ones that you have not stolen from the trial is I show a picture of my son when he was 2 wearing boxing gloves and I show a picture of him when he graduated from college, and that was 20 years. That's how long it took from conceiving, designing, funding, answering the thousand hate mail letters from American urologists, even for the concept. And it took 20 years before we published it. This will never happen again in the U.S. There is no one else to fund it, and there's no one who has the patience and then what we do in prostate cancer is going to have changed. So even if you showed something it might be irrelevant because everyone is going to get fusion MRI with some new imaging thing 20 years from now.

DR. CRAWFORD: But that's--

DR. GARNICK: Yeah, you've got to enrich your population with a population of patients that have a high event rate.

DR. BRAWER: Well what's what I said. I think you--

DR. GARNICK: Then that's not right, maybe that's not right.

DR. BRAWER: You're never going to get it for localized prostate.

DR. GARNICK: Well or you could, well, the genomics could identify people that are going to have a high event rate, biochemical relapse.

DR. CRAWFORD: But they might be the ones that you can't help and so there's the problem with that. I mean I think you've got to, you've got to--

DR. GARNICK: Well those are the ones that need help.

DR. CRAWFORD: Yeah but maybe those aren't--

DR. GARNICK: Those are the ones that need help.

DR. CRAWFORD: Maybe those aren't the ones that, they may need help but may not be the main benefiters of the help. So I mean every time you try to do a study where you enrich it with rapid PSA doubling times or this or that it sort of backfires sometimes on you. I think you've got to be very careful. No, so what's the way forward here? We want ten years when we come back here what do we--

DR. GARNICK: I mean just like you said focal therapy 12 years ago people laughed at it and 12 years later it's a viable option. Within 12 years we see, unless we do something today--

DR. CRAWFORD: I agree but what is it? Tell me what it is. How do we, we're not going to get, we're never going to get another prevention trial because no pharma company unless they feel they want to lose their drug or they got money to burn are they going to do a prevention trial. I mean--

DR. GARNICK: I agree.

DR. CRAWFORD: Nothing against you but you were one the people that killed the finasteride stuff and--

DR. GARNICK: Well, we haven't talked about finasteride and--

DR. CRAWFORD: Well I know and we have - - .

DR. GARNICK: There's a lot more information on finasteride.

DR. CRAWFORD: You and I disagree on that.

DR. GARNICK: I know. I know. I'm just going on the data David.

DR. CRAWFORD: Okay, that's just the way it, there's lots of ways to look at data. But how do we go forward? What do we, what do we, we're not going to do a prevention trial. We're not going to do another screening trial because you can't unless you go to some place in South Africa or whatever where people--

DR. GARNICK: Okay.

DR. CRAWFORD: I don't know. Where are you going to do it? You're not going to do it--

DR. GARNICK: Show that localized therapy is effective in either delaying biochemical relapse, metastasis-free survival, or overall survival in a population of patients that have clinically localized prostate cancer with high risk genomic features. And do a randomized study of treatment versus delayed treatment or treatment versus no treatment. And that's a beginning.

DR. CRAWFORD: We've shown that men that have Gleason 6 cancers and have a radical prostatectomy and have Gleason 6 cancers that out of 15,000 men, 20,000 men only 1 died of prostate cancer.

DR. GARNICK: Okay.

MALE VOICE: - - .

DR. CRAWFORD: Yeah.

MALE VOICE: And that's the rub.

DR. CRAWFORD: I know so what does that mean?

MALE VOICE: Well either--

DR. GARNICK: But you've only had--

MALE VOICE: You know, Gleason 6 is penis, prostate, prostate epithelial neoplasm of--

DR. CRAWFORD: Well - - potential or something.

MALE VOICE: Yeah, yeah significant, or the radical, we don't know the answer but it's - - because there's no randomization. But--

DR. CRAWFORD: Well okay, so my point is that means they treated, they did a lot of radicals on people that really didn't need it. If you've got nobody dying of the disease. Okay?

DR. GARNICK: So you're not going to show a mortality difference there.

DR. CRAWFORD: Right.

DR. GARNICK: Because they'll never die with or without treatment.

DR. CRAWFORD: But the rub is as you said they all had radicals

and the 30% that have Gleason 8's and 9's and 7's in there they had mixed were thrown out.

MALE VOICE: Right.

DR. GARNICK: But this number of--

DR. CRAWFORD: And so did you have to go out and do a lot to, well what you just said, how many breast cancers do you have to treat or screen for to benefit a few?

DR. GARNICK: One patient.

DR. CRAWFORD: And the, I don't know.

DR. GARNICK: I mean that number of only one patient dying of 15,000 of Gleason 3+3 cancer, that's certainly not my experience because obviously in 15,000 people with Gleason 3+3 cancer there's going to be a whole series of those men that had, you know, higher grade disease that was not detected.

MALE VOICE: No, but they had radicals.

DR. CRAWFORD: So they all had radicals and all of the 8's, 9's, and 10's were thrown out.

DR. GARNICK: Okay.

DR. CRAWFORD: That's the problem.

DR. GARNICK: Okay.

DR. CRAWFORD: So the issue is--

DR. GARNICK: So pure 3+3s, pure 3+3s.

DR. CRAWFORD: I mean we're really on the same path, we're just on two different planets about markers. I don't know.

DR. GARNICK: If I were a marker company I would try to embark upon a study that would have a high event rate and basically show that your marker, which led to treatment, which led to an improvement that otherwise would not have been done.

MALE VOICE: It is fine. You just can't randomize it to no treatment. That's the rub.

DR. GARNICK: Well randomize them to Treatment A versus Treatment B.

MALE VOICE: If you have 750 enrolled but I can't remember it, 20,000 or 1 in 10,000, 20,000 I think in the screening register. So the denominator has to be huge to get. I mean it will be interesting to see what happens with - - .

DR. CRAWFORD: With what?

MALE VOICE: The British trial.

DR. CRAWFORD: Yeah.

MALE VOICE: RP versus radical.

DR. CRAWFORD: That data should be out this year, end of this year.

MALE VOICE: Supposedly.

DR. CRAWFORD: Well they have STAMPEDE. Right? And that's a whole bunch of different randomized trials. Right?

DR. GARNICK: Well STAMPEDE was chemotherapy and Zometa.

DR. CRAWFORD: Well no it's not just chemo.

MALE VOICE: Radical versus radiation versus - - .

DR. GARNICK: What?

DR. CRAWFORD: It's a whole bunch of different.

DR. GARNICK: Yeah and Zometa.

DR. CRAWFORD: Abi and huh? Karl, you're just a clap doctor from Iowa that sees a little bit of prostate. What do you think about all of those prostate guys that work for you? what do you think about all of this stuff?

DR. KREDER: Well you know I kind of like what you said yesterday about keeping it simple, and in terms of screening I think I would do something based on the European guidelines and just say everybody gets tested at 50, if it's less than 1 they get tested 60, if it's still less than 1 that's it.

If it's 1.5 then you check them again in a year, two years, whatever interval, but keep it pretty simple and straightforward since most of the screening is going to be done by these failing practitioners. So that's what I would argue for is, and then see how we do going forward.

DR. CRAWFORD: So you would just recommend so at age 50 get your first PSA rates, 45. That's what a lot of people are doing. But there was a, something happened with that whole theory. I forgot what it was recently where it kind of got blown by the wayside.

DR. GARNICK: A lot of high-grade cancers don't like PSA.

DR. CRAWFORD: Yeah I know but there was something else.

DR. GARNICK: It's a problem.

DR. CRAWFORD: I can't--

DR. KREDER: Yeah, but you back it up if it's African Americans, back it up to 40 to 45. But I think it's got to be something very simple, straightforward, easy to follow algorithm.

DR. CRAWFORD: I don't see any more questions. Do we have any other comments or--

DR. GARNICK: No. Dan, any comments?

DR. CRAWFORD: We could actually, we could actually stop early so everybody had a break here or something. Anybody else have anything that, any speakers we missed for today? No? all right, thank you all. What do you want to say?

MALE VOICE: See you at 7:00. See you at 7 o'clock in the--

DR. CRAWFORD: Where is it again now?

MALE VOICE: The Pompeiian which is the mezzanine level of the main building, and dinner will be in the Lake Terrace Dining Room.

MALE VOICE: The same place as last year. Right?

MALE VOICE: Right across.

MALE VOICE: The same place as last year?

MALE VOICE: Actually, we were in the golf club last year. We're right across from the main building.

[Background conversation]

[END Day 3 Session 4.mp3]