*(PLEASE NOTE: Transcribed automatically by Vimeo, mistakes are possible)*

**TRANSCRIPT – 08 06 21** "Advances in Metastatic Prostate Cancer: is Precision Medicine Here?" **Karen Autio, MD, MSc**

* 00:36:52Alright well today I have the pleasure of introducing Dr Karen audio and alum of our internal medicine training here at uva.
* 00:37:00She was one of our first clinical investee or track participants Dr audio completed her undergraduate and medical education at Washington University in St Louis and university of Maryland college park respectively.
* 00:37:13After spending three years here at uva Dr audio traveled north to complete her fellowship and medical oncology at memorial sloan kettering cancer Center.
* 00:37:22Dr audio joined the Faculty at sloan kettering in 2013 and has risen to the rank of system professor in the department of medicine.
* 00:37:30Dr audio has established herself as a multi faceted academic clinician heavily engaged with resident and fellow education, while, on the gpu service at sloan kettering and mentoring, a wide breadth of mentees at varying stages of training.
* 00:37:45where she has carved out her most important role is in the clinical research rena Dr audio is the site sponsor and primary investigator for seven different phase one and two studies investigating novel treatments for metastatic.
* 00:37:57castration resistant prostate cancer diagnosis that carries significant short term morbidity and mortality.
* 00:38:04hector audios work in particular focuses on new applications of immune checkpoint inhibitors and metastatic castration resistant prostate cancer, as well as novel study drugs for this disease.
* 00:38:14doctor audience clinical work and research exists as the frontier of treatment and management of prostate cancer, and it is a true honor to have her back here at uva i'll be at virtually to give grand rounds on precision medicine and prostate cancer.
* 00:38:28With that i'll hand it over to Dr audio.
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**Karen Autio**

00:38:31Great Thank you so much for that kind introduction in it, it really is an honor to to be back i'll be at virtually with you guys today so i'm going to go ahead and.

* 00:38:41share my screen.
* 00:38:52See.
* 00:39:07Can you guys see my slides now.
* 00:39:14Sorry, I think everyone's on mute so just give like a thumbs up if anyone has a visual.
* 

**UVA Internal Medicine**

00:39:18Guy looks great.

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**Karen Autio**

00:39:19Right okay terrific alright, so today i'm going to be focusing on advances in Meta static prostate cancer, with a focus on those that would fall under the umbrella of precision medicine.

* 00:39:32These are my disclosures.
* 00:39:36So precision medicine is defined by the national cancer institute as a form of medicine that uses information about a person's genes, proteins and environment.
* 00:39:44To prevent diagnose and treat disease in the case of metastatic prostate cancer what we're really talking about is using.
* 00:39:52predictive biomarkers that can help guide or therapy options and today i'm going to talk about some of those molecular defined.
* 00:39:59Precision biomarkers but i'd also like to focus a bit on a protein that be, can be used to predict for response and that's psm a or prostate specific membrane antigen.
* 00:40:12So just for background it's important to know sort of how we think of the disease spectrum of prostate cancer, because it really is pretty unique.
* 00:40:21We use something called the clinical States model which is sort of.
* 00:40:25visually represented here, and so, if you were to to sort of take a man who initially was diagnosed with localized prostate cancer.
* 00:40:33And then suffer from a recurrence of that cancer that he ultimately succumb to this is sort of the natural history of the disease, that you would see kind of going from from left.
* 00:40:43To right so again, initially, a man might be diagnosed with localized prostate cancer.
* 00:40:49let's say he has radiation treatment or surgery, and then at some point, after that his PSA starts to rise, and you get conventional scans with a cat scan and a bone scan and you don't actually identify sort of where the recurrence is.
* 00:41:03that's a clinical state referred to as biochemically recurrent disease for men with high risk biochemical recurrence they ultimately will progress to sort of overt metastatic disease that you can see, on standard imaging.
* 00:41:18metastatic disease in that setting is typically responsive to hormonal therapies or medications that lower testosterone called androgen deprivation therapy.
* 00:41:29However, as part of the natural history of the disease there ultimately is resistance those therapies that's developed and that's called castration resistant prostate cancer and what i'll focus on today are really those therapies in that castration resistant prostate cancer category.
* 00:41:47So a little bit of the basics of prostate cancer, this is very much a hormonally driven disease, so the backbone of therapy is what's called androgen deprivation therapy or ATT.
* 00:41:58And we accomplish this by using generate analogs so either generate antagonist that sort of directly blocks and then leads to decreases and lh and fsh.
* 00:42:10With subsequent lowering of testosterone or we use a partial generate agonist which actually initially causes.
* 00:42:17An increase in La fsh an increase in testosterone and then it's only via sort of a negative feedback loop that you get lowering of testosterone levels.
* 00:42:27So when we use these partial agonist it's really important that we do them in conjunction with other anti androgen is to try to mitigate against this testosterone slayer response.
* 00:42:40So the I mentioned the sort of backbone of therapy is androgen deprivation therapy i've listed here some of the sort of most common toxicities or side effects and mental experience.
* 00:42:51In many ways, they're similar to when women go through menopause so hot flushes is very common fatigue loss of libido.
* 00:42:59weight gain was central at possibly is coming with adt some men will have cognitive effects or psychological effects like irritability or cheerfulness.
* 00:43:08As well as gynecomastia all of these sort of short term toxicities can proceed into long term while on androgen deprivation therapy.
* 00:43:17But there are some other kind of more unique long term toxicities that that we monitor patients, for, and that includes decreases in the bone density, with a propensity for Osteoporosis increased cardiovascular risk.
* 00:43:31Potentially with higher lipid levels being one mechanism, as well as potentially some cognitive impairment that can be seen with adt in the long term.
* 00:43:42So, while all these toxicity certainly can affect patients, quality of life for the most part, I would say that these side effects are manageable and adt gets certainly can be very effective.
* 00:43:54at different stages in the disease, so in the initially in sort of localized disease setting if a patient is has high risk prostate cancer, you know it's likely to occur.
* 00:44:05They usually will receive androgen deprivation therapy is sort of fixed course, along with the radiation treatment.
* 00:44:11We use adt on an intermittent basis for men with biochemically recurrent disease so sort of blocks of time on.
* 00:44:18ATT allowing the PSA to drop it they're not restarting again until her PSA rises, however, when men get to sort of overt metastatic disease that you can see, on imaging at that time point.
* 00:44:30androgen deprivation therapy is us sort of continuously, even when at alone is not enough, we don't actually take it away we just add on other therapies sort of on top.
* 00:44:43So I mentioned that for prostate cancer it's usually quite sensitive to androgen deprivation therapy, but at some point.
* 00:44:50Generally around 18 months after the start of adt, although it can vary from months to years a man will ultimately develop castration resistant prostate cancer castration resistant disease is really the lethal form of of prostate cancer.
* 00:45:06So castration resistant disease is really referring to disease that is growing, despite therapies that are lowering testosterone to sort of castrate or very low levels.
* 00:45:17There many sort of mechanisms of resistance that that can explain castration resistant disease, and that includes even though you can measure testosterone sort of.
* 00:45:28In the blood and it can be very low, we know if the tumor level the androgens can be higher.
* 00:45:33A lot of the action is happening at the androgen receptor which can be overexpressed or just sort of consecutively active.
* 00:45:42There are other Co regulatory proteins that are important and castration resistant disease, as well as different proliferative pathways like the p three K and torque pathway.
* 00:45:54So there are a couple of different sort of drugs that have been developed, initially in the setting of castration resistant prostate cancer.
* 00:46:03And this sort of falls into two general categories all they're all kind of lumped into this term called androgen receptor signaling inhibitors.
* 00:46:11So one category is androgen biosynthesis inhibitors and there's really just one drug in that class is called abiraterone it's a SIP 17 lice inhibitor.
* 00:46:21And then the second general category is androgen receptor inhibitors sort of directly blocking the ar and there are a few different drugs that i've mentioned on the slide that fall into this category that includes as a little of my APP glutamate and darryl.
* 00:46:35So, while all of these drugs these androgen receptor signaling inhibitors are initially developed for men with castration resistant disease.
* 00:46:44Through a series of trials over the last five years, we now understand that using these agents, not in combination, but sort of as as monitor therapy with adt are actually.
* 00:46:56More effective if you start them when the disease is actually sensitive to ATT alone so they've sort of moved up in the in the sort of natural history or disease spectrum for prostate cancer.
* 00:47:09We see real variability in terms of responses PSA responses with androgen receptor signaling inhibitors.
* 00:47:18So this is a slide sort of demonstrating three different types of responses, we can see and PSA is on the on the y axis there so.
* 00:47:26The sort of clear as case of a patient who's benefiting is somebody represented on the green curve that's.
* 00:47:33A patient has a quick sort of PSA decline was starting in androgen receptor signaling inhibitor and then that is a durable response.
* 00:47:41On the flip side, you can see, and read the somebody who's sort of a non responder who has primary resistance to an androgen receptor targeted therapy therapy is a might have an initial decline or us.
* 00:47:54But it's very brief and then the PSA quickly starts derives.
* 00:47:58In the middle represented and blue is what we might call the drifter, so this is somebody whose PSA will.
* 00:48:05decline with starting and androgen receptor signaling inhibitor and then it just sort of slowly starts to creep up and that might not be associated actually with any radiographic.
* 00:48:15progression for quite some time, so these are responses.
* 00:48:20reflective of men who are sort of naive to androgen receptor signaling inhibitor was the first time they received on they've only been on ATT kind of prior with castration resistant disease.
* 00:48:32If we were to look at a plot of men who had been on one androgen receptor signaling inhibitor and then switch to another.
* 00:48:40overwhelmingly what you would see is that red pattern and non responder pattern, because the mechanisms of resistance against one ar signaling inhibitor are usually very similar to a to a second.
* 00:48:55So I want to spend a moment just to talk about the androgen receptor itself through really kind of for functional domains to it there's the amino.
* 00:49:04terminal transcription will domain, a DNA binding domain, the hinge region, and then the car boxy terminal login binding domain.
* 00:49:15Right now, all of the androgen receptor inhibitors bind at that leg and binding domain, and this is sort of problematic for these treatment emergent androgen receptor mutations that can develop.
* 00:49:28Such as one called ARV seven, which is one of the best studied mutations, because in that situation, this the terminal domain is actually absent, so the ar is sort of consecutive and the active it's constantly signaling and there's no direct is going to be able to sort of block that.
* 00:49:48This is a study from a number of years ago that looked looked at sort of ARV seven status of patients.
* 00:49:57To see what their responses there PSA responses were like on on different therapies lb seven in this situation was.
* 00:50:06Measured off of circulating tumor cells, which are epithelial tumor cells that sort of shut off from metastatic or primary sites so on the left hand side that ends luda might.
* 00:50:18graph if you see a little Gray dagger That means the patient had previously received abiraterone and on the other side on the androgen.
* 00:50:27biosynthesis inhibitor or apparatus around if you see a little Gray dagger if that patient had previously received as a little mind.
* 00:50:35So when you can see, is for those patients that had this ARV seven splice variant overwhelmingly the PSA is are rising with with treatment.
* 00:50:46And ultimately in this study it sort of demonstrated that know patients that had a are the seven really have a significant response or benefit from an androgen receptor signaling inhibitor.
* 00:51:00So this poses a big challenge for our field and there's a lot of efforts being looked at how can we target these ar mutated cancers so some strategies that are being.
* 00:51:11evaluated are can we change the binding site, for example, to the N terminal domain, can we inhibit a transcription will sort of co-factor like.
* 00:51:19Some of these being done with these bet inhibitors or can we actually just degrade the entire androgen receptor and there are a couple of different mechanisms that are being looked at.
* 00:51:29One is selective androgen receptor graders and another as a therapy called a protest or protein slices targeting time arrows.
* 00:51:39So protests work by essentially tagging that target protein in this case, they are with a three ubiquitous in like cases and then they sort of lead that target protein.
* 00:51:48To be degraded by the proteasome and the parties own graves, the target protein into lots of small peptides and, importantly, these compounds can be recycled, so you can you can sort of recycle or you can rather degrade you know multiple ar.
* 00:52:06ar V 110 is sort of a first in class protect that pre clinically at least targets wild time androgen receptor as well as some applications of the ar.
* 00:52:18There was a phase one clinical trial looking at this particular protect that was able to demonstrate about two out of 15 patients.
* 00:52:27Having clear benefit so that's not really an overwhelming response to out of 15, but it certainly is kind of proof of concept and there's a phase to trial of this drug that is ongoing.
* 00:52:40So are these new era targeted therapies really precision medicine, I would say, probably not are not yet, because most of the trials.
* 00:52:48Looking at these ar D graders are similar types of drugs don't require a specific ar mutation as part of eligibility.
* 00:52:57And it's more so the biomarker development that's being done retrospectively looking at results that we're learning.
* 00:53:04True biomarker selection or sort of true precision medicine, looking at a or mutations would require identification of that biomarker in advance, usually through a prospective biopsy or looking at a circulating tumor cell.
* 00:53:19So this is a busy slide it's meant to represent sort of across the different clinical states of prostate cancer, the various sort of FDA approved therapy options.
* 00:53:32And there's kind of two take home points to the slide the first is to say we have lots of different sort of drugs that target different mechanisms of action.
* 00:53:42In prostate cancer that can be very effective, so I mentioned the androgen receptor targeted therapies, we also use chemotherapy and prostate cancer immunotherapy parp inhibitors and reading pharmaceuticals.
* 00:53:55The second kind of take home point as i've highlighted in red all of those therapies that are very much biomarker driven that fall into this category of precision medicine and then the remainder of our time, oh i'll focus on those therapies.
* 00:54:11So when most people think of precision medicine they think about you know how can we use genomic data to guide our therapy options.
* 00:54:18And when we talk about genetics there's two broad categories, we can either look at the germline or hereditary that's important not only for identifying.
* 00:54:27mutation that might have therapeutic impact for a patient but also what's called cascade testing so testing family members that might also be at risk drumline testing can also oftentimes alter preventative care for other malignancies.
* 00:54:42The second type of testing that's most commonly thought of is somatic testing so that's testing of the tumor itself, and this is used to identify whether or not somebody hasn't mutation.
* 00:54:54for which you would stay change their Stanford prepare options and we'll talk a bit about bracket to mutations and perp inhibition.
* 00:55:01Sometimes identification of a mutation is purely just for prognostic importance there's not necessarily a therapeutic advantage to it.
* 00:55:09And then there's certainly a whole host of investigation or therapies that are driven by a biomarker selection so.
* 00:55:15For example, a patient has a mutation and pathway X and we've got a drug out there that's targeting that pathway.
* 00:55:22In in a more extreme example of precision medicine is personalized truly personalized individualized medicine, such as personalized cancer vaccines.
* 00:55:33So this is when you basically biopsy the tumor sequence the DNA and then throughout sort of complex algorithm you try to identify which new antigens can listen and immune response and do Hla screening alongside.
* 00:55:49And ultimately, these these new antigens are you know peptides are sort of used to create the vaccine which is then administered to the patient.
* 00:55:58The personalized cancer vaccine approaches is is exciting it's really only been looked at and relatively small studies, not yet specifically in prostate cancer.
* 00:56:10Okay, so I want to focus a bit on DNA damage repair, because it is a big breakthrough and for prostate cancer.
* 00:56:20So genomic instability is a hallmark of cancer, we know that the DNA is damaged, you know thousands 10s of thousands of times.
* 00:56:28per day and ourselves are relying on repair mechanisms to function, and if the cell is unrepaired then it dies.
* 00:56:36The same is true for for tumor cells most cancer cells do have a dependence on these DNA damage repair pathways This is important because, if we can identify a DNA damage repair alteration.
* 00:56:49In prostate cancer, then we can actually exploit this therapeutically for these sort of tumor specific vulnerabilities.
* 00:56:58So you know much of the mutational landscape in prostate cancer came out of these multi institutional efforts.
* 00:57:06This is one such effort that came out the stand up to cancer grant whereby about 150 different metastatic biopsies from men with prostate cancer.
* 00:57:18underwent whole excellent sequencing and transcription of profiling, not surprisingly, one key finding was that about 63% of men had a mutation in the androgen receptor but also importantly about a quarter of men had some sort of alteration in DNA damage repair.
* 00:57:39This is another series that we conducted at memorial sloan kettering that looked at about 500.
* 00:57:46biopsies using an in house platform that's FDA approved called Ms K impact in this series we looked at mentor throughout the natural history of prostate cancer so men with localized prostate cancer through metastatic disease both.
* 00:58:02Hormone sensitive and castration resistant disease and, as you can see, for the metastatic biopsies these were largely from left note, but also a somewhat significant proportion from bone and fewer from this role metastatic disease sites.
* 00:58:20In the Ms K series it sort of replicated what had been seen and other series so about 27% of men had an alteration bracket one bracket to ATM or check to these are all DNA damage repair alterations and you know roughly 20% or so of men have a germline alteration as well.
* 00:58:42So the reason why these bracket mutations are so important to identify is because of poly adp rivals polymerase or parp.
* 00:58:50inhibitors which sort of exploit these cell deficiencies so normally if there's a single strand break in the DNA, the purpose i'm will come in and it will repair the DNA.
* 00:59:04When there's a parp inhibitor in place that single stream break is going to turn into a double strand break.
* 00:59:10So for our normal cell with that double strand break it will evoke homologous recombinant repair to fix the cell and the cell will survive this is a tumor cell we're talking about.
* 00:59:22So with parp inhibitors and a patient who has a deficiency in homologous recombinant repair what will happen is that cell will not be repaired and ultimately the cell will die.
* 00:59:35So.
* 00:59:37One of the first parp inhibitors that was approved initially and breast and ovarian cancer is a drug called elaborate.
* 00:59:44And this was a study done in prostate cancer with this drug called the profound trial.
* 00:59:50It was a study where by all patients were required to have a deficiency in homologous recombinant repair and then they were randomized to the one to receive either elaborate.
* 01:00:01or physicians choice and there was crossover allowed for those patients randomized control arm, so that they could get access to elaborate.
* 01:00:10Importantly, the sort of physicians choice was either wasn't androgen receptor signaling inhibitor it was either apparatus owner and solidified.
* 01:00:20And then, this patient population, they all had had at least one androgen receptor signal inhibitor previously, so we knew the responses wouldn't be particularly good for the physicians choice whether or the control arm.
* 01:00:33The primary endpoint for this trial was reading graphic progression free survival because again these patients were allowed to have crossed over.
* 01:00:43The results of the profound trial showed that perp inhibition could significantly delay metastatic disease progression and as well as prolong life on the order of about four months extension in overall survival relative to the control arm.
* 01:01:01there's another parp inhibitor that's FDA approved it's called mukhabarat in this is what we call a PSA waterfall plot, so this is again PSA declined shown on the.
* 01:01:13y axis, and you can see, these are for patients with bracket one in bracket to alterations that overwhelming the therapy essays are are declining with therapy.
* 01:01:25In contrast, however, when you look at recap read in other homologous recombinant repair deficient deficient sort of mutations.
* 01:01:35And the non bracco one two cohort the responses are much less impressive with many patients not showing any clear benefit in terms of PSA response, most of the patients in this group had ATM mutations and some check to.
* 01:01:55So the FDA did approve these two parp inhibitors last year, both elaborate, as well as recap.
* 01:02:03recap or was only approved in the bracket one bracket to population, because, as I showed you the non bracket bracket to patients just seemed much less likely to benefit.
* 01:02:15For the elaborate FDA approval, because of the way they designed their trial that actually encompassed 13 different genes.
* 01:02:23So, in summary, you know many patients with castration resistant prostate cancer will farber germline or semantic alterations in DNA repair teens and molecular testing is now standard of care.
* 01:02:35We talked about vocabulary, which is approved for men who've had at least one ar signaling inhibitor and one chemotherapy drug that's just for those with bracco one bracket to alterations.
* 01:02:45For elaborate the FDA approval is larger and covers 13 different teams involved with DNA damage repair, however, we do know that the strongest evidence certainly is in those patients with bracket to alterations and and the other genes, I would say is relatively unproven.
* 01:03:05Both of these drugs are well tolerated and have similar toxicity profiles.
* 01:03:11So is precision medicine with these parp inhibitors really a home run, I think, for those patients with dd ours, the treatment options certainly expand.
* 01:03:21But it is important to know that the overall survival benefit relative to the control arms in these trials are still four months.
* 01:03:28Which is really similar to all of our FDA approved therapies that are unselective in this disease.
* 01:03:35We know that resistance department division is common and it's certainly an active area of investigation, and I think for the field and prostate cancer.
* 01:03:44A lot of the big unknowns are whether or not these drugs are better poised earlier in the disease spectrum so for men who have.
* 01:03:53biochemically record prostate cancer or early hormone sensitive disease or whether we should use these drugs more as maintenance therapies, as well as whether or not they should be used in combination.
* 01:04:08So the the other sort of genomic predictive biomarker response and prostate cancer relates to checkpoint in addition so cells that have abnormally functioning mismatch repair genes are unable to correct those errors and that leads to.
* 01:04:25Basically, these microsatellite unstable tumors that are kind of accumulations of DNA micro satellites are short repetitive sequences of DNA.
* 01:04:37what's unique about these tumors is that these microsatellite on staple tumors is they tend to express a large number of new antigens.
* 01:04:46That can be recognized for the immune system sort of when properly activated I in in the setting of a huge checkpoint inhibitor so back in 2017 the FDA actually approved a drug called federalism as.
* 01:05:02An anti P one agent or a checkpoint inhibitor for any solid tumor with mismatch repair deficiency or microsatellite instability, who had progressed on other lines of therapy.
* 01:05:14In order to assess for mismatch repair deficiency, this can be done via immunities to chemistry or PCR or in the case of prostate cancer is usually done with next generation sequencing.
* 01:05:27Unfortunately, this really only represents about 3% of metastatic prostate cancer, so it is a small proportion of patients that fall into this category.
* 01:05:37The other two normally to find sort of predictive biomarker response to checkpoint inhibition are for those patients that have high tumor mutational burden.
* 01:05:47And this is again and all solid tumor approval not specific for prostate cancer.
* 01:05:54With the sort of a similar rationale these high tea and be tumorous tend to express a lot of new analytics that can be sort of recognized and targeted by the immune system.
* 01:06:04The trial that led to the the sort of all solid tumor approval is called keynote 158 it's a face to trial.
* 01:06:12openly will study international looking at this drug temporal ISM and there were 10 different cancer types that were allowed on the keynote one five day trial prostate cancer was not among them.
* 01:06:23And in this study, they sort of separated patients into either high tea and be defined as a tumor mutational burden.
* 01:06:30Of greater than or equal to 10 mutations for mega LACE versus low TB and what they saw it as the overall response rates were certainly much higher in the high TV category, with an overall response rate of about 29%.
* 01:06:46So when we think about these two all solid tumor indications I think it's important for us in prostate cancer, to understand that.
* 01:06:55Our patients were really under represented in these studies so those collective trials there about six of them all together that lead lead those.
* 01:07:05FDA approvals actually only included one patient amongst those six trials that had prostate cancer.
* 01:07:11So when we want to look at sort of the relative benefit and prostate we're sorta reliant on looking at our own data much of watch is retrospective in nature.
* 01:07:22And there have been several retrospective series looking at miss fast repair deficiency and prostate cancer those do seem to support the use of checkpoint inhibition with patients having PSA declines, as well as benefit in terms of overall response rate and shrinking of tumor.
* 01:07:40For the tumor mutational burden sort of.
* 01:07:45category, there was a trial of symbolism at kind of in all comers with prostate cancer, it was a large face to study.
* 01:07:53It was a disappointing study in many ways that only showed a response rate of about 3% in all comers with prostate cancer, but as part of that trial, they did.
* 01:08:03Look at tumor mutational burden and what they were able to identify is that there was sort of a correlation between tumor mutational burden and PSA response.
* 01:08:17So, in summary, for the new checkpoint inhibitors again they are not approved for all cases and metastatic prostate cancer, but only those that are sort of generically defined under this all solid tumor FDA approval, including.
* 01:08:29mismatch repair deficiency or high tumor mutational burden again this is really a minority of patients with metastatic prostate cancer that that end up falling into these categories.
* 01:08:42So.
* 01:08:43molecular profiling is certainly standard of care for prostate cancer in order to identify these different mutations either a DDR mutation or.
* 01:08:55Even though there are few and far between mismatch repair deficiency or high T and b.
* 01:09:00But we definitely have a lot of challenges, when it comes to next generation sequencing and prostate cancer.
* 01:09:05Some of that is or much of that actually is is related to the fact that.
* 01:09:09For men with prostate cancer oftentimes they're only side of metastatic disease are bone metastases which tend to be sporadic and really kind of low yield for DNA extraction.
* 01:09:21In order to do next gen sequencing so many times clinicians end up sort of resorting to the initial prostate biopsy to do this testing.
* 01:09:31The success rate in bone for next gen sequencing is really only about 40%, so it is a real challenge for our field.
* 01:09:41You know this, this has certainly some challenges when you're trying to look at kind of the most recent mutations.
* 01:09:48For semantic alterations looking at record to loss of function, these do tend to be pretty early events.
* 01:09:56meaning, you can oftentimes find them in the initial prostate biopsy so you're not necessarily missing so much if you have to resort to looking at the at the prostate tumor.
* 01:10:07When it comes to looking at androgen receptor alterations, on the other hand, these are very much treatment related so you're not going to find them if you're looking on the initial prostate biopsy.
* 01:10:18and looking at the metastasis this is really where the action is.
* 01:10:22In order to circumvent some of these challenges with bonus static biopsies we do use what's sometimes called liquid biopsies we're looking at cell free DNA.
* 01:10:32This does require that there's enough sort of tumor burden that you're going to get good capture and then one of the other challenges that that happens with cell free DNA.
* 01:10:41Is this thing called chip or call him out of pieces of indeterminate potential so basically the amount of plastic DNA is the main compartment of cf DNA.
* 01:10:51And just as part of normal aging you'll get some magic mutations nice from plastic cells so sometimes.
* 01:10:59On a on a cf DNA, it might read out that there's an ATM mutation but that's really not you know, an ATM mutation that's driving prostate cancer, it might actually just be an ATM alteration that's part of chip.
* 01:11:12So there, there are many different commercial platforms for reporting both cf DNA, as well as looking at tissue there is not great standardization amongst those reporting.
* 01:11:26platforms and again, you can get sort of trick defeat don't exactly know what you're doing into calling chip or miss classifications of model really versus violet loss.
* 01:11:41Okay, so I want to switch gears a little bit and sort of transition from talking about those molecular defined biomarkers predictive of response to talking about a protein.
* 01:11:52that's predictive of response and therefore sort of falls under the umbrella of of precision medicine in my mind and that protein is called psm a or prostate specific membrane antigen.
* 01:12:03it's really expressed throughout the natural history of prostate cancer from localized through castration resistant disease, and very importantly, it has restricted expression in normal tissues.
* 01:12:16It is typically they're on sort of regardless of the size of metastatic disease, and this is a trance membrane protein, with just a cartoon on the left side of it.
* 01:12:28So the measurement of pma expression has very much evolved over time from you know his to chemistry to circulating tumor cells to what we'll talk about a bit more, which is pet based imaging.
* 01:12:42And this is just a representation of looking at pma standing on immunities to chemistry.
* 01:12:47and see the brown standing of pma it's typically use kind of as a diagnostic tool in this setting and, like all tissue samples are icy there's always the question of whether or not it's representative of sort of the totality of metastatic disease.
* 01:13:05With as a development came circulating tumor cells So these are epithelial cells that are sort of shut off from the primary or metastatic sites.
* 01:13:17And the visualization that you see here is looking at CT sees on a particular platform, called the epic platform, so you have a dad be positive.
* 01:13:27nucleus surrounded by cytoplasm that side of carrot is positive and seeking 45 negative with this particular platform, you can also do some sort of additional.
* 01:13:40staining with PS ma.
* 01:13:43And CT sees or you know, a terrific tool in the sense, just because you know they they can be corrected via peripheral blood so they're very easy, it gives you sort of a snapshot in time of what's going on.
* 01:13:57We use the ctc approach when we were looking at this particular investigational drug that i've shown here it's called binder one for.
* 01:14:05it's a nanoparticle dos attacks will chemotherapy that targets pma and when you can see, is and looking at these psm a positive circulating tumor cells.
* 01:14:16That they were able to, we were able to show that in least in some patients that those psm a CDC has declined the therapy sort of representative of a farmer code dynamic affect.
* 01:14:29what's really transformed our disease with visualizing psm a expression on tumor cells, however, is psm a pet based imaging so this really allows us to visualize kind of all the metastases at once it.
* 01:14:45has potential to really transform many different phases of prostate cancer, perhaps most importantly those men with biochemically recurrent prostate cancer So those are the men who.
* 01:14:57Had a prostatectomy, for example, and then at some point in the man's PSA is rising, you get a conventional cat scan bone scan MRI can't localize where it's coming from.
* 01:15:08This is a place where a PS and a pet can really help guide management options and potentially for radiation therapy.
* 01:15:17PS made pet I think also has a real role in metastatic prostate cancer as a predictive biomarker of response and also if it falls into this category of precision medicine in this sense.
* 01:15:32So, to understand why PS ma pedis is such a breakthrough in prostate cancer.
* 01:15:38requires sort of an understanding of what our current tools are for energy bone metastases.
* 01:15:44So, again with prostate cancer bone is the primary site of metastatic disease and for many men, it is the only side of Meta static disease.
* 01:15:53We are completely reliant on technetium 99 bones and tigger fear bone scans in order to determine whether or not a patient is benefiting from a particular therapy.
* 01:16:05And the challenge with that is that bone scans don't actually measure tumor itself, I mean they measure bone turnover Ostia plastic activity.
* 01:16:14So they sort of measure what's happening in the surrounding bonus result of tumor the tumors are the lesions that should say tend to appear late on bone scans.
* 01:16:24They unfortunately are not measurable so unlike a solid tumor like a lung cancer or you can see a train from five centimeters to two centimeters.
* 01:16:34Put a percentage or an overall response on that that doesn't exist in prostate cancer and prostate cancer with bone scans.
* 01:16:43What we're really looking for is if we see a new lesion were concerned that there's growth but it's really not a situation where you can say, well, it looks bigger and therefore it's worse because you're not actually measuring tumor itself.
* 01:16:57So this has been a real problem for our field for a long time it's impeded our drug development.
* 01:17:04And this is where psm a pet really gives us a lot of advantages it sort of lifts the veil on otherwise a cult disease in many situations.
* 01:17:14This is a comparison of bone scan for patient that looks like he has you know, maybe a single ball metastases in the pelvis.
* 01:17:23as compared to the myth images, the maximum intensity projection images on the psm a pet where you can see there's a lot more diseases there and what you see kind of lining up in the face is the products which do have.
* 01:17:37products and salivary glands which which do have pma expression on them, otherwise the bigger is your senior just the kidneys and the bladder where the tracers being excluded.
* 01:17:48So psm a pet imaging is is still pretty new far field, the first FDA approval for a PM a pet scan actually came in December of this year, sorry of December of 2020 with a second.
* 01:18:04pet based tracer a piece of a pet tracer just FDA approved a couple of months ago for commercial use.
* 01:18:12Importantly, while these two tracers are now FDA approved, they have not been been reviewed by the centers for medicare and medicaid so they are historically not being reimbursed.
* 01:18:25But we hope by first quarter of next year they'll they'll have a ruling your decision as to when these might be.
* 01:18:33reimbursed by insurance.
* 01:18:37Alongside PS may pet imaging comes our first very promising psm a directed therapy it's a drug called.
* 01:18:50It is a beta emitting radio pharmaceutical that is delivered selectively to pma expressing tumor cells and sort of their surrounding micro environment.
* 01:19:03So this is a drug that released its results at asco this year that's sort of a big cancer conference that was about two months ago, at this point.
* 01:19:15And it was a the results came from this phase three international trial, called the vision trial.
* 01:19:21In the vision trial patients were randomized to the one to either received leticia m plus standard of care versus standard of care alone, importantly, all patients who enrolled on this trial had to have PS may positive.
* 01:19:37By pet disease, making this sort of a precision medicine, I think, in that respect these were very heavily pretreated population of patients, so all patients had received at least one androgen receptor signaling inhibitor and at least one taxi and chemotherapy if not two or more.
* 01:19:57chemotherapy was not allowed, as the sort of standard of care.
* 01:20:05And, which is because standard of care was done in combination with blue tissue or in the control arm and there was not any safety data to tell us.
* 01:20:14That chemotherapy could be safely, combined with leticia them so that was sort of the reasoning.
* 01:20:20Patients who underwent cat scans mris and bone scans every eight weeks on trial up until about the 24th weekend which time they transition to every 12 weeks, and they were pre-specified alternate primary endpoints of radiographic progression free survival and overall survival.
* 01:20:37I mentioned that all patients had to meet certain criteria for psm a pet positivity so all patients undergoing a PS may pet scan prior to study entry.
* 01:20:48These pets are all read centrally, to ensure that they met the necessary eligibility requirements.
* 01:20:54and, interestingly about 13% of screen patients were not enrolled because their PM a pet biomarker criteria was not met.
* 01:21:03So while that doesn't seem like a huge number 13% when you think about how many men are potentially eligible for this therapy it's it's thousand, so it is, I think, relevant to ensure that that patients are selected who are most likely to benefit from this therapy.
* 01:21:22The vision trial.
* 01:21:25was when it first initiated it noticed early on that there was actually a very high dropout rate in the standard of care arm, you know 56% of patients were discontinuing.
* 01:21:38Study enrollment you know, shortly after randomization when they realized that they were not going to be randomized to leticia there was no, you know placebo component to this trial.
* 01:21:49So, because of that it certainly has potential to really impact not only the trials integrity, but.
* 01:21:57The the the results essentially of the trial, so what the sponsor did, is it pause the trial be Captain Roman at those sites that had high dropout rates.
* 01:22:08And really provide a lot of site education and communication to try to ensure that this high dropout rate was curtailed.
* 01:22:16In doing so, after the pause in the trial, the dropout rate was significantly less than the control arm, we went down to about 16%.
* 01:22:26You know the The other thing that the sponsor of the trial needed to do was sort of talk with the FDA about how this could potentially impact the.
* 01:22:33The study endpoints so it was decided to the overall survival study endpoint would remain the same, with all patients randomized which makes sense.
* 01:22:43However, for their radiographic progression free survival endpoint they decided that those that that measurement would only began with those patients who had been enrolled after that enrollment pause.
* 01:22:59So the results of the vision trial were positive it did show a significant benefit in both overall survival, as well as free graphic progression free survival.
* 01:23:10On the order of about a four month advantage relative to the control arm for overall survival, so this drug is not yet FDA approved, although we're hopeful that it will be by first quarter of next year.
* 01:23:28I want to talk a little bit about psm a as a target in immunotherapy on it's it's largely been looked at related to oncology vaccines which.
* 01:23:38In prostate cancer has been pretty pretty underwhelming there are a lot of challenges with vaccine development and prostate cancer.
* 01:23:46Including you know a lot of deficits in sort of antigen presentation or down regulation of anti see complex.
* 01:23:53prostate cancers oftentimes thought of as sort of an immune desert with not a lot of activated T cells.
* 01:24:00So these have all kind of been big barriers for us in vaccine development and prostate cancer There is however kind of a new generation of immunotherapy and prostate cancer that's looking very promising.
* 01:24:14And this is just a cartoon of several of those types of therapies, including by specific T cell engages.
* 01:24:22trikes which is kind of redirect natural killer cells to tumor associated antigens or cartoons or kinetic androgen receptor T cell therapies.
* 01:24:31You know some of the big advantages of these types of therapies, like the bite therapies are that they're able to bypass that initial.
* 01:24:40requirement of T cell receptor mhc kind of interaction for for activation of the immune system they also don't require expression, if I may see on the on the target cell.
* 01:24:53They tend to have sort of low effectively target ratio is needed to successfully sort of kill a tumor cell as well.
* 01:25:04This is one.
* 01:25:06representation of a by specific T selling gauge your it is essentially showing us that the target is both the CD three and a body, as well as the psm a expressing tumor cell it basically brings these two.
* 01:25:24cells close together and allows for this really tight immune sin Apps where you can get sort of T cell activation.
* 01:25:31kind of a release of cytokines and ultimately license of tumor cells another mechanism whereby these bite therapies are are sort of postulated to be beneficial is with antigen spreading.
* 01:25:46or episode spreading so you're essentially expanding the T cells and it's causing activation against these various tumor antigens not necessarily just the target antigen psm a.
* 01:26:01There have been results released for one of these particular PS macd three bite therapies that I wanted to highlight because it's it's really pretty encouraging it's with a drug called.
* 01:26:14User results that were presented from their phase one dose escalation trial, this was with a population of patients that was.
* 01:26:23Very treatment refractory all had had multiple androgen receptor signaling agents all have been required to have chemotherapy.
* 01:26:31Several of these patients had actually received new tissue on clinical trials as well.
* 01:26:36And what this phase one dose escalation portion was able to demonstrate was that about two thirds of patients did achieve a PSA response with about a third of them having a PSA response of greater than 50% their baseline.
* 01:26:54We participated in this trial at sloan kettering and I thought i'd just highlight one of my patients responses to this particular.
* 01:27:02bite therapy, so this is a gentleman who, when he he 77 when he was initially diagnosed he hadn't been a static.
* 01:27:10Disease, so he sort of de Novo metastatic at the time of his initial diagnosis with bone metastases he received androgen deprivation therapy and upfront ever our own.
* 01:27:21treatment he progressed on that ultimately received radium two to three, which is radio pharmaceutical progressed on that receives docetaxel chemotherapy progressed on that and then went on to this particular clinical trial.
* 01:27:35As part of this trial patients were getting psm a pet based imaging, which is what i'm showing on this slide So you can see his to his PSA.
* 01:27:44Prior to starting on Sunday was about 18 he had a number of bone metastases including some in the thoracic spine that were sort of continuous with the rib.
* 01:27:54And also pelvic bone mets after the first month on treatment his PSA dropped to about to a bone related pain, he had prior to study.
* 01:28:05had resolved, and then by week 12 his PM a pet imaging essentially shows that these psm a expressing areas had had pretty much resolved indoor substantially reduced so it's um it's a modality of therapy that we're we're excited about in the field.
* 01:28:27The toxicities associated with these by specific T cell engages are, however, not insignificant.
* 01:28:34And the primary side effect is something called say to kind of release syndrome or CRS this is really an on target effect related to the binding of the antigen antibody and sort of subsequent bystander immune.
* 01:28:47reactions it really leads to this sort of massive release of pro inflammatory cytokines with release of interleukin six and interferon gamma as a result of this CRS oftentimes requires a new patient management to help support these patients.
* 01:29:07The clinical manifestations of CRS in many ways are similar to sepsis so patients can have fever and riders that can become hypertensive and need IV fluids, and sometimes visa oppressors there to kip Nick tech a card deck.
* 01:29:24They can have a number of different guests for intestinal side effects as well, like diarrhea and nausea and the management of CRS again it's it's overwhelmingly sort of supportive.
* 01:29:36And it's different than the management of immune checkpoint inhibitors that I imagine, many of you have.
* 01:29:42have treated Those sort of toxicities with steroids, and we actually try to avoid the use of CRS of sorry of steroids with CRS.
* 01:29:50For concern that it could affect the the advocacy of the drug we will use drugs like tosa lose man, which are anti oh six agents, because of sort of the mechanism of CRS.
* 01:30:06So with precision medicine is it is it better with less toxicity, I would say there's certainly as a greater likelihood of responses, the biomarkers is present.
* 01:30:17In terms of less side effects, I think, in general, yes for purpose ambition there certainly is less sort of off target effects for the PS may directed radio live in therapy, we spoke about new tissue 617.
* 01:30:32There is less off target effects, you will get some direct on target effects like Dr now from the psm expression on the salivary glands.
* 01:30:42For immune checkpoint inhibitors the while those toxicity certainly aren't chemotherapy and it generally is better tolerated, however.
* 01:30:50There are those unique immune related adverse events and then for these PS may directed by specific, Sir, and you know therapies again they're certainly not the typical chemotherapy side effects, however CRS can be quite significant, and it is sort of an on target effect.
* 01:31:10Okay, so my take home points today, hopefully i've been able to convey to you that precision medicine is certainly.
* 01:31:18being widely adopted and management of metastatic castration and resistant prostate cancer to guide our therapy options.
* 01:31:24We spoke about molecular profiling or genomic testing to identify those patients with DDR alterations that might benefit from a perp inhibitor.
* 01:31:33We spoke a bit about checkpoint inhibition for those few patients with prostate cancer, who have mismatch repair deficiency or high tumor mutational burden.
* 01:31:41And then, lastly, we touched on psm a pet as a imaging biomarker to select for those that have PM a positive disease, either with tissue which is not yet FDA approved or some of these immuno therapies that are currently under investigation.
* 01:31:59Thank you, I know I have like a minute left right.
* 

**UVA Internal Medicine**

01:32:07Thank you so much structure audio that was wonderful and if anyone has any questions that they want to send through the chat or we have people in the audience here guys have any questions for Dr audio.

* 01:32:25um one question I had was about the p i'm going to pee MSA.
* 01:32:31or pma if that has any utility as a screening tool, or if you tend to only see the horizon and metastatic disease.
* 

**Karen Autio**

01:32:40So it's it is being incorporated, not so much as a screening tool, but for one sort of.

* 01:32:48place where they'll they'll go for indication is for men with you know high risk localized prostate cancer, you know so many of those men do end up recurring after after surgery.
* 01:32:59And some of that's probably because they had metastatic disease at that time of their initial diagnosis, where the conventional scans made it look as though they were localized.
* 01:33:07But they really were not so that is not so much screening, but for initial diagnosis of high risk localized diseases and other place where the psm a pet imaging is is being evaluated.
* 

**UVA Internal Medicine**

01:33:22With their next question testing, I know you said that it standard of care to get up front, but it seems like most of the therapies, that you would use based off of it or more like second, third line therapy.

* 01:33:35Why, why is it that its standard of care to get it immediately and why is it not something that we're saving for these people that aren't responding to initial therapy.
* 

**Karen Autio**

01:33:42yeah great question, and I should clarify.

* 01:33:46The for the treatment options is once they hit metastatic disease that we typically do it, however, for germline testing, there are indications.
* 01:33:57For men that have high risk prostate cancer or if they meet certain categories of you know, family history or ashkenazi Jewish descent, where you would check for germline testing earlier.
* 01:34:09But you're right for the targeted therapies absolutely it's actually it's once a man has metastatic prostate cancer that those are typically being evaluated.
* 

**UVA Internal Medicine**

01:34:18Okay, thank you, we have a question in the chat do you foresee psm a down regulation by tumor cells as a mechanism of resistance to psm a directed therapy or has this been documented, I asked, because this may appear as responsive following PSA PMs a pet.

* 

**Karen Autio**

01:34:36yeah no it's a it's a great question and we have seen in the loop tissue and clinical trial that.

* 01:34:45Some patients when they ultimately stop responding to nutrition we'll do that on the basis of psm a negative disease, so it may well be that we are or driving in different sort of beast at that point with psm a negative prostate cancer.
* 01:35:06Almost.
* 01:35:06Asians will progress with just psm a positive disease as well, so it's.
* 01:35:10Very expect.
* 

**UVA Internal Medicine**

01:35:13All right, well it's one o'clock Thank you so much for really interesting lecture we really appreciate you taking the time.

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**Karen Autio**

01:35:19Thank you.

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**Unknown Speaker**

01:35:21Take care.