It's my pleasure to be host today.

I'm Roy herbst.

Today, we're very fortunate we have Doctor Daniel Petre lack who’s professor of medical oncology and urology and the leader of our GPU program.

He spent many years at Columbia University.

Before he was recruited here,
now 7 plus years ago, almost eight and Dan is really, you know, been a leader in urologic cancers,

Just in the last year with some of his major studies working with the PROTAC with Crag Cruzen Arvinas Anthy in fortunate event and in bladder cancer. Published in the new internal medicine to name a few. He is a world leader. In this area, he’s also built a team in Geo Oncology that is putting patients on protocol and raising the bar.
for these diseases around our care centers and around our entire network and at the main center. So then we're really excited. You know, one of the things we've been doing lately is having the different dogs presented grand rounds as a chance to sort of integrate. You know, the clinical translational program with the basic science and hopefully will have a plenty of time today for discussion. And with that I'll turn it over to you. Dan, and thank you for coming today.
Thanks Roy. It’s it’s a pleasure being here today and thank you for inviting. You know it’s actually about nine years. It’s going to be September of 2012 that I came on board and it was the best decision I’ve ever made from a career standpoint. And I thank you and all the leadership of the Cancer Center for being supportive over the years. And a lot of the work we’re going to present here today was done by our group, including jochim, Mike Hurwitz, and but I’d like to give a first a little bit of an overview as to what is going on in prostate cancer.
and how do we think about it. 
So as we know, prostate cancer is really two different diseases. There’s the disease that you die with, and this is the prostate cancer die from the Gleason 6 carcinoma, which is not none really. In some editorials have been thought to not to be even a cancer. There was some thought about taking away from that particular classification that was in the JC a couple of years ago. That’s none. That’s really not going to cause a patient’s demise. Even 90% chance of being biochemically free.
A relapse at five years, no matter what local therapy you go forth with, we’re going to focus today on the castrate resistant disease. And it’s important to think about this disease in terms of clinical states. As I mentioned before, there’s a clinically localized prostate cancer which can be cured with local treatment despite local treatment. No matter what you receive with its radiation therapy, hormonal therapy about one in three men in unselected cases will have a rising PSA.
This can result in a biochemical relapse or eventual clinical metastases, which is the hormone sensitive state. In the non castrate disease, as we see in the upper portion of this particular slide you also can have a rising PSA without metastatic disease and this group of patients is somewhat problematic and and when you install hormone therapy because there’s some men that may never need to go on engine deprivation therapy and this of course has significant side effects including weight gain, loss of muscle mass, fatigue, loss of sexual function.
So this can have a significant impact on the patient's quality of life. It's questionable whether implementation of hormone therapy at this state will improve survival. We then go on to the clinical metastases in the castrate state and there are multiple treatments that we have available and eventually we have pre chemotherapy and post chemotherapy patients. The landscape has changed and I think the important thing to remember is that this was at Doctor Charles Huggins presentation above prize in 1966. He was the person that discovered that.
prostate cancer is a hormone sensitive disease that if you give androgens the disease will be stimulated. But this is not curative, despite regressions of great magnitude is obvious that there are many failures of endocrine therapy to control the disease in cirrhotic that some of the greats of prostate cancer, including Doctor Huggins, actually died from Ictact disease themselves. So this is how we look at the disease in 2021. If you think back to 2004 when Docetaxel was approved was pretty simple, you had one treatment and this was useful
NOTE Confidence: 0.75882185
00:05:06.498 --> 00:05:08.970 for metastatic castration resistant disease.
NOTE Confidence: 0.75882185
00:05:08.970 --> 00:05:11.666 And then you went on to 2nd hormones
NOTE Confidence: 0.75882185
00:05:11.666 --> 00:05:14.917 or or two to palliative bodies antra.
NOTE Confidence: 0.75882185
00:05:14.920 --> 00:05:18.056 Now we have a variety of different
NOTE Confidence: 0.75882185
00:05:18.056 --> 00:05:20.149 treatments immunotherapy which will be
NOTE Confidence: 0.75882185
00:05:20.149 --> 00:05:22.515 talking bout with sipuleucel T as well
NOTE Confidence: 0.75882185
00:05:22.515 --> 00:05:25.127 as other agents agents that affect.
NOTE Confidence: 0.75882185
00:05:25.130 --> 00:05:27.150 DNA repair other chemotherapeutic agents,
NOTE Confidence: 0.75882185
00:05:27.150 --> 00:05:29.418 as well as other hormonal agents
NOTE Confidence: 0.75882185
00:05:29.418 --> 00:05:31.590 that show improvements in survival.
NOTE Confidence: 0.75882185
00:05:31.590 --> 00:05:33.610 But the key point is,
NOTE Confidence: 0.75882185
00:05:33.610 --> 00:05:36.711 is that we're not curing anybody with
NOTE Confidence: 0.75882185
00:05:36.711 --> 00:05:39.060 this particular approach and the
NOTE Confidence: 0.75882185
00:05:39.060 --> 00:05:41.420 meeting survival is generally about
NOTE Confidence: 0.75882185
00:05:41.420 --> 00:05:43.765 increments of anywhere between three
NOTE Confidence: 0.75882185
and five months in this situation.

So with this massive data, how do I like to think about this disease?

Well, like to think of this in terms of classes of agents. We have really 4 main classes that we use from a therapeutic standpoint for castration resistant disease. Namely, immunotherapeutic agents such as Sipuleucel T. Pember lose map for a small percentage of patients will be talking about a few minutes hormonal agents. Castrate resistant disease retains its hormonal axis and if you look at androgen receptor expression.
in specimens from patients,

castration resistant prostate cancer,

you'll find that about 90\% still

have an active androgen receptor

axis and we're going to exploit

that with some of these agents.

In fact,

it's known that some of the

chemotherapeutic agents, such as docetaxel,

may actually work by hormonal mechanism.

What do we mean by that?

Well,

when you bind testosterone

to the Android receptor,

it has to translocate the New
York nucleus and microtubules are essential to the transport of that particular complex into the nucleus. I mentioned cytotoxic agents such as docetaxel and cabazitaxel, their isotopes that damage DNA, radium 223. We're not going to get into those, but focus of investigation recently have been part inhibitors such as elaborate Kappa rib and that’s appropriate for about 10 to 20% of patients with castration resistant prostate cancer. So we’ve been behind the long investigators as well as the breast.
period of time we’ve used clinical characteristics to determine how we sequence our agents. Symptomatic versus asymptomatic, the tendency was to give hormonal therapy to those patients who had. Who are asymptomatic and safe chemotherapy for later? That may not be the right way to sequence patients visceral versus non visceral disease and then pre and post those heat. Axel was initially used as a way of approving drugs for castration of resistant prostate cancer.
The other issue, now which is coming into play as we’ve seen in breast cancer and I’m not going to go into the specifics of this, but agents which have been used traditionally to treat castration resistant disease have been moved up into the hormone sensitive state. And is actually a greater improvement in the hazard ratio when drugs such as, Hazard ratio is about .6. It’s pretty significant so so that state will affect what you’re going to be doing in castration resistance because the resistance patterns may be different, and we’re only going to start seeing
now how that may influence the treatment

Because the downstream effect only started about three to four years ago.

So as I mentioned, we’ve been behind our colleagues in lung cancer and breast cancer and using targeted therapy and molecular markers and the three, I’m going to focus on today or the androgen receptor, those of DNA repair, and immune markers such as microcycle instability. So immune therapy is an
FDA approved category.

Four of the treatment of metastatic castration resistant prostate cancer and the agent that’s approved in the United States is something called sipuleucel T.

So this is an ecologist T cell product that’s made by taking the patient’s own immune cells, culturing them with a fusion protein that uses both prostatic acid phosphatase and GM-CSF. Fusion protein prostatic acid phosphates expressed about 90% of prostate cancer cells, so this is very specific to prostate cancer. This APC takes up this particular antigen. It’s presented on the surface and
you have a fully activated T cell by the time this is reinfused back to the patient three days later. So the impact trial was published in 2010 and this took patients who had had prior chemotherapy. All forms of treatment and randomize them to receive sipuleucel T or a placebo. And it was shown that there was significant improvement in overall survival in the patients who received this particular product. It was about the hazard ratio 0.775.
to classic chemotherapy trials.

You did not see an improvement in progression free survival and that led to a lot of skepticism initially because the PFS did not correlate with OS. Objective responses and soft tissue are infrequent. Now again, this is a select group of patients, so those patients were entered in. The study had bone only disease or a minimal lymph node disease. They did not have visceral disease. He really couldn’t see whether there was a response, but generally the soft tissue
00:10:58.170 --> 00:10:59.866 disease did not respond.

00:10:59.870 --> 00:11:01.330 PSA responses were rare.

00:11:01.330 --> 00:11:02.790 We do see them.

00:11:02.790 --> 00:11:04.980 We do see predominantly PSA stabilization,

00:11:04.980 --> 00:11:07.740 but despite this we do see a correlation

00:11:07.740 --> 00:11:10.009 between the PSA quartiles at study

00:11:10.009 --> 00:11:12.277 entry or on this particular trial.

00:11:12.280 --> 00:11:14.800 So those with low PSA’s have higher

00:11:14.800 --> 00:11:17.177 hazard ratios of survival or better

00:11:17.177 --> 00:11:19.625 hazard ratios than those with high

00:11:19.625 --> 00:11:21.977 PSA’s and again leading to the fact

00:11:21.977 --> 00:11:24.736 that we want to use immune therapy

00:11:24.736 --> 00:11:27.748 early in the course of disease.

00:11:27.750 --> 00:11:30.142 So for number of years we tried to

00:11:30.142 --> 00:11:32.439 explain why this happens and Ravi Medan
00:11:32.439 --> 00:11:34.790 at the NCI is actually published.
NOTE Confidence: 0.8302439
00:11:34.790 --> 00:11:36.800 A very very elegant paper in
NOTE Confidence: 0.8302439
00:11:36.800 --> 00:11:38.140 the oncologist in 2010.
NOTE Confidence: 0.8302439
00:11:38.140 --> 00:11:39.830 Looking at the differences in
NOTE Confidence: 0.8302439
00:11:39.830 --> 00:11:41.520 terms of how we look
NOTE Confidence: 0.8165383
00:11:41.597 --> 00:11:43.823 at outcomes and in an immune therapy
NOTE Confidence: 0.8165383
00:11:43.823 --> 00:11:46.070 as well as cytotoxic therapy.
NOTE Confidence: 0.8165383
00:11:46.070 --> 00:11:50.320 So on the Y axis we see tumor burden X axis,
NOTE Confidence: 0.8165383
00:11:50.320 --> 00:11:53.015 the time. And as we see here,
NOTE Confidence: 0.8165383
00:11:53.020 --> 00:11:55.449 we expect the patient to be progressing
NOTE Confidence: 0.8165383
00:11:55.449 --> 00:11:58.039 rapidly if you give cytotoxic therapy,
NOTE Confidence: 0.8165383
00:11:58.040 --> 00:12:00.833 you have a decline in your tumor
NOTE Confidence: 0.8165383
00:12:00.833 --> 00:12:03.209 volume or two to our burden
NOTE Confidence: 0.8165383
00:12:03.209 --> 00:12:05.757 and then you see a take off.
NOTE Confidence: 0.8165383
00:12:05.760 --> 00:12:07.705 Once they become resistant and
NOTE Confidence: 0.8165383
00:12:07.705 --> 00:12:10.468 often you see a parallel or an
increased slope to what you’ve seen.

When these patients were prior to their chemotherapy.

With immune therapy or vaccine therapy, what you tend to see is a blunting of that PSA curve.

So what you’re actually doing this, but potentially missing progression events or seeing progression events and missing an overall effect.

So really, the hazard ratio is what I think is important, and the overall three year survival, and unfortunately with the sipuleucel T trials they did not
follow patients past three years,
00:12:39.969 --> 00:12:41.909
NOTE Confidence: 0.8165383
and I've actually been after the company
00:12:41.910 --> 00:12:44.346
NOTE Confidence: 0.8165383
to look at that particular question.
00:12:44.346 --> 00:12:47.169
NOTE Confidence: 0.8165383
to see whether there is a
00:12:47.170 --> 00:12:49.162
difference in five year, survivals.
NOTE Confidence: 0.8165383
00:12:49.162 --> 00:12:52.020
NOTE Confidence: 0.8165383
The question of molecular markers, well,
00:12:52.020 --> 00:12:54.444
NOTE Confidence: 0.8165383
immune therapy with PDL one,
00:12:54.444 --> 00:12:57.676
NOTE Confidence: 0.8165383
and prostate cancer,
00:12:57.680 --> 00:12:58.892
NOTE Confidence: 0.8165383
really doesn’t have a great response rate.
00:12:58.892 --> 00:13:01.720
NOTE Confidence: 0.8165383
Generally about 5 to 10% at best in terms
00:13:01.720 --> 00:13:05.356
NOTE Confidence: 0.8165383
of objective response in unselected patients.
00:13:05.356 --> 00:13:07.780
NOTE Confidence: 0.8165383
So this is a study that came out of
00:13:07.780 --> 00:13:10.759
NOTE Confidence: 0.8165383
Memorial Sloan Kettering Cancer Center,
00:13:10.759 --> 00:13:13.430
NOTE Confidence: 0.8165383
looking at 1033 patients who had
00:13:13.430 --> 00:13:15.746
NOTE Confidence: 0.8165383
MSI high in prostate cancer.
00:13:15.746 --> 00:13:17.880
NOTE Confidence: 0.8165383
It’s only about a 3%.
Yeah, but hit rate with that particular marker. But what’s interesting is that you can see this, develop overtime that if you look at sequential specimens in patients with castrate resistant prostate cancer, you can see up regulation or development of MSI. So this is something that you really do need to check regularly and in our patients with castrate resistant disease and also seven of those 32 MSI high patients had a dream sideline mutation in Lynch’s assistance.
Syndrome associated gene.

Does this have an effect on response to checkpoint inhibition therapy?

The answer is yes. This is their series.

Looking at both PDL one as well as PD.

One inhibitors and castrate resistant disease and about half of patients will have objective soft tissue responses and a higher percentage of patients will have PSA declines.

So in my opinion, and I think that many thought leaders feel the same way,

all patients with castrate resistant prostate cancer need to be checked for microsatellite instability.
Pember Lism AB is an FDA approved drug in this state of disease and this it can be administered in those patients who have that particular marker.

 Rushan ion has looked at CDK 12 in these patients in castrate resistant patients as well as we know, BIALLELIC mutations are formed a distinct class of prostate cancer.

 This leads to genomic instability as well as the development of neoantigens, and rule is also demonstrated with this particular marker that you can see increased T cell infiltration and.

 Also, responses in men with
castrate resistant prostate cancer.

So we actually LED a phase one study of atezolizumab, an castrate resistant disease. This was published in clinical Cancer Research earlier this year. Joe Kim and I were coauthors on this patient.

This particular study and we had two different cohorts. In initial phase, one cohort of 10 patients, and then a 15 patient expansion cohort. As we can see here, the response rates with a Tesla some were somewhat disappointing. About 50%.

These are patients who had multiple.
Prior chemotherapies or immunohormonal therapies and we did see a fairly good meeting survival of 14.7 months, but this is unselected and there were two partial responses by resist criteria. Overall now we tried to look for Molecular characterization that may lead us to understand better why these patients responded. We saw some higher levels of CD8 We did not see any significant PDL one expression, nor did we find microsatellite instability. And this is one of our responders
who is microsatellites.

Table had really not a particularly higher level 22 mutation rates.

But he did have a mutation in ATM which you know.

Again, there been others. Some others have correlated responses with these DNA repair enzymes,

but this was really 2 number too small to make any great conclusions.

So where are we moving and immunotherapy yellow? And what’s or some of the trials that are open right now?

Well, we’ve been looking at it, Ralph, up with a bio excel and
this is in resistant patients, both newer, castrate resistant as well as small cell carcinoma of the prostate. Looking at DP 8-9 inhibition with the Excel 701201 combined with the volume in this trial is ongoing and occurring patients right now. Joe Kim in the Phase one group. Is looking at a novel combination of ateez allusion mab, along with cables, and which is a TKI which is which actually was originally looked in. Prostate cancer number of years ago. But really, a failed phase, three studies.
And as we saw before, it is losing members and 8% response rate cables got a 5% response rate. You put the two of them together. They’ve got a 30% response rate and Joe is working in the phase. One group is also designing a phase one study to look at biological markers. Small select group of patients with this combination, we’ve completed a vaccine study of APSA construct with Tremolux Moab. The interesting thing about this trial, it was just presented yesterday. Tasco is that we saw responses in patients who are hormone sensitive.
00:18:07.701 --> 00:18:09.449 with a rising PSA.

00:18:09.450 --> 00:18:11.766 Really didn’t see any really significant activity in castrate resistant disease,

00:18:11.766 --> 00:18:13.800 but unless we did have a couple of responses were still looking some

00:18:13.800 --> 00:18:16.768 of the biologic korelitz and then.

00:18:16.768 --> 00:18:18.924 Finally.

00:18:18.924 --> 00:18:21.600 We completed accrual in a phase three trial of Docetaxel plus and


00:18:22.002 --> 00:18:24.414 We completed accrual in a phase three trial of Docetaxel plus and


00:18:26.991 --> 00:18:29.146 Now I mentioned before that in the castration resistant state you still

00:18:29.146 --> 00:18:31.668 see a positive result of that particular study.

00:18:31.668 --> 00:18:34.038 Now I mentioned before that in the castration resistant state you still
00:18:40.914 --> 00:18:43.302 have an active androgen receptor and
NOTE Confidence: 0.7329831
00:18:43.302 --> 00:18:45.406 there could be a different number
NOTE Confidence: 0.7329831
00:18:45.406 --> 00:18:48.020 of ways in which we can see this
NOTE Confidence: 0.7329831
00:18:48.020 --> 00:18:49.540 receptor receptor become activated.
NOTE Confidence: 0.7329831
00:18:49.540 --> 00:18:51.096 In fact, Jack Keller,
NOTE Confidence: 0.7329831
00:18:51.096 --> 00:18:54.858 who was actually in the lab till his mid 90s,
NOTE Confidence: 0.7329831
00:18:54.860 --> 00:18:57.900 believe it or not who was at UCSD,
NOTE Confidence: 0.7329831
00:18:57.900 --> 00:19:00.938 was one of the first people to
NOTE Confidence: 0.7329831
00:19:00.938 --> 00:19:03.868 describe the fact that if you took.
NOTE Confidence: 0.7329831
00:19:03.870 --> 00:19:06.090 Prostate cancer specimens an measure
NOTE Confidence: 0.7329831
00:19:06.090 --> 00:19:08.310 them for testosterone after these
NOTE Confidence: 0.7329831
00:19:08.380 --> 00:19:10.600 patients had undergone either chemical
NOTE Confidence: 0.7329831
00:19:10.600 --> 00:19:12.820 or physical castration that you
NOTE Confidence: 0.7329831
00:19:12.890 --> 00:19:15.482 would find that there was increased
NOTE Confidence: 0.7329831
00:19:15.482 --> 00:19:17.210 levels of testosterone overtime.
NOTE Confidence: 0.7329831
00:19:17.210 --> 00:19:18.810 So there’s an interesting
pathway of androgen synthesis.

There are also alternative splicing mechanisms.

There’s aberrant function these mutations, which will give you gain of function, which will talk about in a few moments. But all these particular pathways can lead to deregulation of the androgen receptor despite the fact. There are serum levels of testosterone that are castrated. So one way that we can overcome this of course, is shutting down testosterone synthesis completely.
Testosterone is predominately made with from the testicles, but as I mentioned before, the prostate cancer cells can make their own testosterone as well as the adrenals that is actually about 20% of all the testosterone is created so you drink or text to peripheral tissues. You can shut down these particular pathways by 1720 lyase inhibition with a drug called abiraterone. And this is the chemical structure of Apparate, Rhone. There’s a second way of blocking the Android receptor pathway, which is FDA approved.
And that’s using anti androgens which directly antagonized the receptors enzalutamide was rationally designed from a series of different compounds that was selected for androgen receptor antagonism. The interesting thing about this drug, although overtime it’s been shown that we see very very we see this occasionally is that there’s no known agonist. Activity see this occasionally with patients. There is some of these anti androgens when you stop them. The PSA actually goes down and we
still have not been able to correctly explain that particular effect.
So you can decrease testosterone levels and block the receptors.
Now the fact is these both of these drugs are FDA approved. They both improve survival again by about three to four months.
As we’ve seen before. Do we sequence them because these drugs in terms of toxicity, seemed to be less toxic than giving attack scene such as kabasi, Taxol, docetaxel, unfortunately? This cross resistance between these agents PSA responses are generally 10 to 20%,
and you see a progression free survival of about three to four months.

If you sequence Abby after ends or ends after Abby.

And also refining to that, taxing's are less effective and vice versa. These drugs are also less effective.

Act after Taxing's and there may be some slight cross resistance.

So kimchi at University of Vancouver is actually summarized this data, and if we look across the board as I mentioned before, we see a survival of 8.7 about 12 months.
If you give these drugs sequentially. And PSA decline rates of 20 to 30%, whereas the single agent drugs are about 50 to 60% overall. So how do we look at this in terms of resistance? I mentioned before, you could have upregulation of different pathways. And particularly CYP 17 you could also see these splice variants. You can see induction of glucocorticoid expression that also may be related to enzalutamide resistance, so they again are multiple pathways that we can go forth with.
One is error V7.

Play RV 7 is a truncated version of the androgen receptor.

The Android receptor has three different components.

One is the DNA binding region, the other one is the liggen binding region and then the other is the hinge region.

So the login biting region is deleted in a RV 7 so this can be constituency activated and then 'cause activation of the androgen receptor pathway.

It has to dimerize.

So that’s actually important fact as we see here.
From this particular slide, this is from my colleague Daniel Interactice at Johns Hopkins. If you look at those patients who are AR V7 negative versus those who are very 7 positive, they have a better progression free survival when you’re treating these drugs in patients with abiraterone enzalutamide, you also better PSA responses. So if you make a RV 7. You’re less likely to respond to these particular drugs now. Taxing’s are a little bit more responsive, but the response rate with taxes or not as good.
But again, you see a difference between the RV, 7 positives and the negatives, but overall taxes do have a better response in those who are positive, so this data was performed in patients with CTC’s so. This is associated with primary resistance. The positive patients may still become sensitive to taxanes, but in positive men, taxanes may be more effective. Acacius and there may be comparative efficacy with targeted agents in the negative patients compared to the.
The these next generation ages, such tabron enzalutamide. So this leads us to a trial called card.

And this is important political implications to our patients because What Car did was it took patients who had received abiraterone or enzalutamide for one year or less, then went on to receive docetaxel. And of course, the dilemma that physicians have in the situation is whether you treat with an alternative anti androgen or to give a chemotherapy agent such as cabazitaxel. And this trial,
I think, lends credence to the fact that these AR V7 mutants may actually persist for a period of time, because if you give a second androgen signaling agent so the opposite agent, if they’ve got abiraterone first, then they get enzalutamide. If they get enzalutamide, then they get abiraterone. You have a better survival with cabazitaxel then with the secondary agent, and that’s both in terms of progression free as well as overall survival.
at the hazard ratio of 0.64.

So in sequence we tend to use chemotherapy earlier in these patients.

So what are we working on at Yale?

That may be a way of moving forward with this particular pathway?

Well, number of years ago?

Roy, you know,

one of the things I think.

You need about Yale, and I think the pandemic is really.

As really hurt is this seminar we used to have on Tuesday afternoons between the chemistry department and the Medical oncology department.

Roy was really instrumental in getting
this going forward forward and Craig Crews came up to me at one of these meetings and said you have a need for Brooke drugs and prostate cancer, and it’s absolutely he’s would you want to go forth with another hormonal age. And I said absolutely, there’s room for that because there’s a mechanistic approach to it, and it turns out that the company that Craig previously had founded. CEO had died from metastatic prostate cancer, so he was on a mission to find other agents and this was really the perfect collaboration between
a bench and Ben’s bedside.

So this is a novel drug.

This is a RV110 and what’s the science behind this?

Well, we’re trying to degrade the proteins, so there’s a natural pathway.

The proteasome pathway, which we basically can degrade

Soap Protex are ways of basically accelerating this ubiquitin based pathway,

proteins with a bug within our body.

Soap Protex are ways of basically accelerating this ubiquitin based pathway,

so you have a disease causing protein.

E3 ubiquitin ligase will bind to that.

The Pro tech will actually accelerate

that and then this induces

ubiquitination of the target protein.
And this, I think the neat thing about this drug is it’s recycled. You can have as many as 400. Throat androgen receptors proteins that can be taken out by this pro tech. In a given cell and then it basically is destroyed by the protein cell. So why is this called a dumbbell? Well, this is the shape of it. There’s a protein login domain which is the warhead targets a specific protein. It’s linked to the ligase Lagann which recruits the E3 ubiquitin ligase and so all three of these
play a role in protein degradation.

So how is this related to prostate cancer with a RV?

110 is a pro tech that targets the engine receptor.

So as we mentioned before, you can have amplification and receptor mutations and this was developed both in androgen resistant as well as sensitive cell lines.

So there are variety of different mutations that this pro tech will degrade the T878H75Y the F877L and MV895 point mutations but not L 2702 an AR V7.
So does that mean that it’s not going to work in these particular subtypes? The answer is no because if you look at Doctor Interactice paper carefully for New England Journal of Medicine you’ll find that in addition to having the air B7. This usually amplification of and wild type receptor which could be affected by the different Protex. So this may also affect amplification of the wild type receptor as we see here. It’s going to degrade 90% of the engine receptor in vitro.
So two years ago we opened up the phase one study that looked at AR V110IN men with castrate resistant prostate cancer. They had to have at least two prior therapies. We did not basically eliminate those patients who had extensive treatment. We had required that they have either abiraterone or enzalutamide. It took us a little while to get to the 140 milligram dose, which is what was important in the laboratory to achieve activity. So this is the minimal efficacious dose.
00:29:54.273 --> 00:29:56.933 140 milligrams or greater orally.
00:29:56.940 --> 00:29:58.750 So here’s some some evidence
00:29:58.750 --> 00:30:01.120 that we are hitting the target.
00:30:01.120 --> 00:30:03.598 This is a patient of ours that
00:30:03.598 --> 00:30:06.035 was treated with ARVs 110 and we
00:30:06.035 --> 00:30:08.621 have both a baseline and it big
00:30:08.621 --> 00:30:10.881 posttreatment biopsy that shows
downregulation of the Android receptor.
00:30:10.881 --> 00:30:15.054 Remember these are heavily
00:30:15.054 --> 00:30:15.726 pretreated patients.
00:30:15.730 --> 00:30:18.089 This is our presentation from last year.
00:30:18.090 --> 00:30:20.365 We see that there is one patient
00:30:20.365 --> 00:30:23.153 out at 35 weeks of duration of
treatment and we did see responses.
00:30:25.760 --> 00:30:28.898 As measured by a PSA decline,
we saw two patients with PSA declines of at least 50% and. Lo and behold, these patients had degradable engine receptor mutations T87A at 875Y.

And we see here that that one patient with the RV 7 did have a very minor PSA decline, but he also had a concomitant mutation. So are responding. Patient here at Yale head.

Multiple treatments, including docetaxel, abiraterone, radium and enzalutamide, he had eight 7597-A mutation
and he had a 74% PSA reduction after his treatment was administered and his time of the presentation is. Duration of response was 30 weeks. This is a patient from Nick Vogelsang at Nevada, also with a very with the same mutation pattern showing a PSA reduction of 97%. And soft tissue responses. So where are we going with this particular treatment? We still have two. We have a phase two trial with two open sub cohorts. Those patients who harbored a RT
7-8 or 75 mutation were taking up

20 patients were still accruing,

and those patients who received

a prior second generation and

androgens and no prior chemotherapy.

The subgroup, one subgroup force are now close to accrual.

At least there an accrual hold it.

This particular point,

so hopefully will open those

in the near future,

and I’d like to know the last minutes

of this talk talk about some of Jochems

work in with with PARP inhibitors.

As we know,

DNA repair mutations are present
in about 10% of patients with castrate resistant prostate cancer. These are predominantly bracket one and bracket twos, but we see a variety of other other mutations such as ATM check too. Powerbi Tunan rad 51. As we know, Prop inhibitors work by the mechanism of synthetic lethality where this is involved in single stranded DNA repair, whereas other agents are involved in double stranded breaks and the two of them combined together can cause synergy. So elaborate has been evaluated.
In castration resistant prostate cancer in a phase two trial, this was published in the journal by Joe Johann de Bono's group, 49 patients. Overall, the response rate was 32.7% when they went back retrospectively looked at genomic analysis. They found that third of 14 of those 16 patients with DNA repair mutations responded. Where is only two patients who did not have that repair mutation responded.
This led to the profound trial which looked at aerolab rib. And two different cohorts of patients, both those who are a bracket, one bracket, two or ATM positive, or other DNA repair mutations in these patients were randomized to receive either a lap RIV or physicians choice of therapy. The trial did meet its primary endpoint, which was radio graphic progression free survival. This was in the bracket one bracket, two or ATM cohorts. There was about a four month difference in radio graphic progression free survival,
and when you look at all cohorts of DNA repair, there was about a two month difference, but the hazard ratio was 0.49. Now this I think is one of the important slides from this. This paper we see that those patients who have ATM mutations really don’t have a particularly great response to PARP inhibitors. In fact, their hazard ratio is one for death, and that’s that’s really different than what we see with the bracket. One and bracket twos and the PR2 3RA’s actually do worse with partition.
This is the survival from the trial. We see that there is an improvement in overall survival. The ratio is 0.64 with a big difference in response rate (33% vs. 2.3%). So this drug is FDA approved. The second FDA approved drug is recap rib in a slightly different group of patients, whereas patients in the profound trial were either refractory to chemotherapy or two next generation. And this study was a phase two trial, not a phase three trial that led to accelerated approval.
In those patients who had DNA repair mutations, who would be progressed after either a Apparate Ronan’s little mind or apalutamide? As we see from this slide here, predominantly have those patients who have bracket one bracket choose an. Not surprisingly, a similar response rate with CAP ribbon. The Bracco Bracco one bracket use 44% but again the same pattern. No real difference in no objective responses in those patients have ATM mutations and the same as far as biochemical responses concerned 51% bracket one bracket,
two said at least a 50% PSA decline.

Where is none, had declines in ATM.

So in this time just click add a little bit and think about what we’ve been thinking about it.

Yale in terms of strategy as far as how we can potentially improve the OR at least expand the use of part numbers. Well, there are variety of different agents that will synergize with PARPAN inhibitors in in vitro. These include Becca Mecca, PR, 3 kinase inhibitors,
androgen receptor pathway.

That is, we’re planning a trial of abiraterone but also antiangiogenic agents and Joakim is and his also looked at the trial of elaborate combined with Sadir nib Ancaster resistant disease, as we see here, it’s an inducer of hypoxemia, Sadir treatment. Patient treated cells do have more hypoxi than the vehicle, and we know that elaborate works in about 10 to 20% of all prostate cancer patients. And from the data from Doctor Bender’s laboratory in preclinical data showing that angiogenesis may be involved.
the combination of elaborate and steered

have seemed to be moving illogical

and come forth with this was for a

presentation at ASCO early ask AGERE

earlier in the year looking at a

randomized phase two trial comparing

each different arms of the study.

These were patients with a median

We wanted to look at this in

retrospective pet fashion. This is.

Was spearheaded by Joseph Kim.

Overall, we enrolled 90 patients nationally,

in the combination.

Each of the each different arms of the study.

These were patients with a median
00:37:38.802 --> 00:37:40.430 PSA of about 60.
NOTE Confidence: 0.75593275
00:37:40.430 --> 00:37:42.872 They could have had prior anti
NOTE Confidence: 0.75593275
00:37:42.872 --> 00:37:44.500 androgen such as abiraterone,
NOTE Confidence: 0.75593275
00:37:44.500 --> 00:37:46.540 enzalutamide and also prior chemotherapy.
NOTE Confidence: 0.75593275
00:37:46.540 --> 00:37:49.305 So these again are heavily
NOTE Confidence: 0.75593275
00:37:49.305 --> 00:37:51.517 pretreated group of patients.
NOTE Confidence: 0.75593275
00:37:51.520 --> 00:37:54.145 So if we look at the prevalence
NOTE Confidence: 0.75593275
00:37:54.145 --> 00:37:56.920 of DNA or repair mutations,
NOTE Confidence: 0.75593275
00:37:56.920 --> 00:38:00.970 overall 31% had some form of
NOTE Confidence: 0.75593275
00:38:00.970 --> 00:38:04.378 DNA repair mutations,
NOTE Confidence: 0.75593275
00:38:04.380 --> 00:38:06.431 either bracket one or bracket 2.
NOTE Confidence: 0.75593275
00:38:06.431 --> 00:38:07.930 The trial did meet its primary endpoint
NOTE Confidence: 0.75593275
00:38:07.930 --> 00:38:10.296 in unselected patients progression.
NOTE Confidence: 0.75593275
00:38:10.296 --> 00:38:15.354 Free survival was better in the combination
NOTE Confidence: 0.75593275
00:38:13.100 --> 00:38:15.354 but we started looking at the data.
We see some patterns which I think could lead us to where we can go forward with this particular approach. We don’t see really an improvement in progression free survival in those patients who are HR proficient. We do see that in the deficient ones, be interesting to see whether it does seem to be somewhat better than what we see with the POP inhibitor alone. But there does seem to be in a very small number of patients. Some response in those patients at least improvement in PFS in those patients or ATM positive.
So this may be lead for future investigation as one would expect in such a small trial like this, you're not going to see a survival benefit, but there is, you know. But again, this is something we need to look at in the properly powered study so it really does summarize. We see a difference in the combination therapy in terms of progression, free survival and exploratory analysis is seeing that that in these particular subgroups there does seem to be an improvement in our PFS, so this is something I think this
00:39:26.873 --> 00:39:29.190 speaks plourd further in this disease,

00:39:29.190 --> 00:39:31.488 so leave some time for questions

00:39:31.488 --> 00:39:32.254 so conclusion.

00:39:32.260 --> 00:39:34.155 All patients with castrate resistant

00:39:34.155 --> 00:39:36.474 prostate cancer in terms of molecular

00:39:36.474 --> 00:39:38.640 markers need to be evaluated for

00:39:38.640 --> 00:39:40.380 DNA repair enzymes mutations.

00:39:40.380 --> 00:39:42.300 As well as Microsoft instability

00:39:42.300 --> 00:39:45.110 program should be used early in the

00:39:45.110 --> 00:39:47.175 course of castration resistant disease.

00:39:47.180 --> 00:39:49.562 Air V110 has clinical activity in

00:39:49.562 --> 00:39:50.753 metastatic castration resistant

00:39:50.753 --> 00:39:51.580 prostate cancer,

00:39:51.580 --> 00:39:54.380 and then we both elaborate in recap,

00:39:54.380 --> 00:39:56.984 rip are approved in these patients

NOTE Confidence: 0.75593275
with castration resistant disease
and we're looking forward to going forth with novel combinations to expand the spectrum of patients who may be eligible to receive part. In addition, I’d like to thank all of our colleagues, I know if miss people in this, but but Joakim Mike Hurwitz, inheritance Bondy, who have really contributed greatly and work real hard in moving these trials forward. Our research associates, particularly Shelby Carleo and Ebony Williams, who helped to see the patients, manage the data. And really,
they're invaluable to our operation map.

Piscatelli leftists about two weeks ago,

but Kristen Fleshman has really done a great job and in helping us out during this time period.

I know I've missed a bunch of different people in this area that have really helped us, and I apologize.

Apologize to those who have not included in this slide,

so Roy,

thank you for your attention and turn it over to questions.

OK thanks Dan. What a wonderful Tour de force in Geo Oncology I'll start.
00:41:03.450 --> 00:41:05.760 Please put your questions into the chat.
NOTE Confidence: 0.8008387
00:41:05.760 --> 00:41:08.320 But yes, we used to call it the cancer chemistry colloquium.
NOTE Confidence: 0.8008387
00:41:09.760 --> 00:41:09.760 And we used to have that on Tuesday afternoons up on the hill. Scott Miller, the chair of Chemistry at the time, and, you know, we organize that.
NOTE Confidence: 0.8008387
00:41:12.048 --> 00:41:13.946 That’s when Julie Boyer was here, you know that you’ve set up.
NOTE Confidence: 0.8008387
00:41:13.946 --> 00:41:15.892 You have a good patient population.
NOTE Confidence: 0.8008387
00:41:15.900 --> 00:41:17.568 You have a good patient population.
NOTE Confidence: 0.8008387
00:41:17.570 --> 00:41:19.250 That’s when Julie Boyer was here, and I’m glad to hear that the pro
NOTE Confidence: 0.8008387
00:41:19.250 --> 00:41:21.514 tech where it came out of that.
NOTE Confidence: 0.8008387
00:41:21.514 --> 00:41:23.429 So my question for you is how can
NOTE Confidence: 0.8008387
00:41:23.430 --> 00:41:25.510 we do more of these here at Yale?
NOTE Confidence: 0.8008387
00:41:25.510 --> 00:41:27.899 Then you have a great mechanism for clinical trials.
NOTE Confidence: 0.8008387
00:41:27.900 --> 00:41:29.568 You know that you’ve set up.
NOTE Confidence: 0.8008387
00:41:29.568 --> 00:41:30.402 You have a good patient population.
What are the next step next agents coming through Yale Science? Do you think? Well, I mean, I think that there’s. There’s a next generation pro tech. That looks more active potentially than a RV. Then the every 110 and we’re moving forth with that in the phase one trial, but I think that the real next generation will be had a sequence. These had to combine these using our tumor bank to understand how to use these particular drugs. I think also. I didn’t really get into this during.
the talk, but but how can we use? How can we include other ethnic groups in our treatments?

It’s actually an interesting phenomenon. There have been publications looking at response rates in or survival to chemotherapy, immune therapy and next generation hormone therapy in African Americans. And it’s actually better. And so we need to get the word out that these trials are open, that all should be included and that we don’t want to see. People missed their opportunities to get drugs that they can move forward with,
but I was really surprised to see that this data we’ve actually been involved with this since our original swax these 2004 when we saw a very very big difference in favor of African Americans with docetaxel chemotherapy. Numbers were too low to make any real conclusions, but Susan Hobby is actually published on this with combined databases and this is something we really have to be to move forward with in terms of understanding how patients respond.
in my interim role here in the CTO, it’s been quite noticeable to me that we do need to have more diversity in our populations and that means reaching out and building trust. And I know you’ve been doing some of that. You know, with the cultural ambassadors and other groups and providing navigators, we have a question from Darrell Martin. Renee, do you want to unmute Darrell so he can ask the question himself? Well, actually I can ask you ’cause you just raised your hand. OK, any other questions for Dan Dan tell
me a little bit about your Darden. Now with Isaac Kim coming as the new chair of Urology, any plans to forge some new collaborations you know? Build out the multi modality presence? Well, I’ve had a couple of conversations already. You know he’s he’s really been one of the Champions. In looking at. Local treatment in terms of patients who have metastatic disease, so this actually has been known for quite some time. In fact, one of the sister presentations
that original meeting at presentation of the texture data at ASCO demonstrated those patients who had a radical prostatectomy. As part of their history did better with chemotherapy than those who did not, and this may be a selection factor, but this has been observed by numerous investigators. It was with this with him to evaluate local treatment in terms of metastatic disease. Through these patients receive a radical prostatectomy. Often my patients will ask me that question should they get local radiation treatment.
It’s actually part of some of our treatment regimen’s already to begin with.

So he’s going to bring a unique look at this particular area, and we’re going to be collaborating on those trials as brothers as well as some other trials that will be targeting the androgen receptor.

Excellent excellent yeah.

He’s already called me as to move start moving it through the CTL so we started OK.

Each young Kim had a question.

Dan at the time of castration resistance, either primary or secondary, do we do?

We routinely sequence AR androgen receptor?
So I've been running, you know, routinely running this as part of a platform because we're looking to select these patients for the trial as part of routine clinical practice. The answer is no. I do not look at and receptor mutations or AR V7 and the reason why I don't look at it is that the. We do the trial that extra micro, which was RPI on this particular study number of years ago of a drug called Glitter Own, which was supposed to be active in a RV. which was supposed to be active in a RV. 7 positive patients an the selection criteria where RV 7 positive
NOTE Confidence: 0.8559534
00:46:27.953 --> 00:46:29.685 ITI and minimally symptomatic
NOTE Confidence: 0.8559534
00:46:29.685 --> 00:46:30.984 or asymptomatic disease,
NOTE Confidence: 0.8559534
00:46:30.990 --> 00:46:33.699 and then this is what killed study
NOTE Confidence: 0.8559534
00:46:33.699 --> 00:46:35.847 because those patients who are air
NOTE Confidence: 0.8559534
00:46:35.847 --> 00:46:37.982 V7 positive tend to be sicker and
NOTE Confidence: 0.8559534
00:46:38.058 --> 00:46:40.028 have more rapid progression than
NOTE Confidence: 0.8559534
00:46:40.028 --> 00:46:42.252 those patients who are in who.
NOTE Confidence: 0.8559534
00:46:42.252 --> 00:46:42.756 Or not,
NOTE Confidence: 0.8559534
00:46:42.756 --> 00:46:44.520 so I’m not going to really waste
NOTE Confidence: 0.8559534
00:46:44.582 --> 00:46:46.232 time on an anti androgen that
NOTE Confidence: 0.8559534
00:46:46.232 --> 00:46:48.141 I know doesn’t work such as
NOTE Confidence: 0.8559534
00:46:48.141 --> 00:46:49.645 abiraterone enzalutamide go directly
NOTE Confidence: 0.8559534
00:46:49.645 --> 00:46:52.260 to chemotherapy and we saw that
NOTE Confidence: 0.8559534
00:46:52.260 --> 00:46:55.035 from the card trial before.
NOTE Confidence: 0.8559534
00:46:55.040 --> 00:46:57.098 So I think that sequencing should be
NOTE Confidence: 0.8559534
00:46:57.098 --> 00:46:59.527 done in terms of clinical trials in
NOTE Confidence: 0.8559534
00:46:59.527 --> 00:47:01.387 terms of understanding the biology,
NOTE Confidence: 0.8559534
00:47:01.390 --> 00:47:03.728 but not right now in terms of
NOTE Confidence: 0.8559534
00:47:03.728 --> 00:47:04.730 routine clinical practice.
NOTE Confidence: 0.77731293
00:47:05.480 --> 00:47:07.034 Thanks Dan, I see that Doctor
NOTE Confidence: 0.77731293
00:47:07.034 --> 00:47:08.480 Bothwell has his hand raised.
NOTE Confidence: 0.77731293
00:47:08.480 --> 00:47:10.664 How do you want to unmute and well,
NOTE Confidence: 0.77731293
00:47:10.670 --> 00:47:12.308 I have you asked your question.
NOTE Confidence: 0.795827
00:47:15.770 --> 00:47:16.920 When they will unmute you.
NOTE Confidence: 0.7467469
00:47:23.180 --> 00:47:24.728 The fear still muted.
NOTE Confidence: 0.8805553
00:47:30.320 --> 00:47:32.468 OK, any other questions or comments?
NOTE Confidence: 0.8805553
00:47:32.470 --> 00:47:34.630 So this has been really great.
NOTE Confidence: 0.8060155
00:47:36.810 --> 00:47:39.002 Then tell us a little bit about you
NOTE Confidence: 0.8060155
00:47:39.002 --> 00:47:41.215 know the network or most of the trials
NOTE Confidence: 0.8060155
00:47:41.215 --> 00:47:43.599 open at at at the different sites.
NOTE Confidence: 0.7994135
00:47:44.210 --> 00:47:46.562 So we’ve been trying to focus on
what’s the best way to balance things in terms of our portfolio, so we are the phase three type trials or open should be open at the clip. That care centers we did have the Taxotere Pembroke trial open and we do have a Pembroke enzalutamide study open as well at some of the care centers. So we’ve been trying to expand those trials that are would normally be seen. In practice, we doing more. The phase one is tripe type trials. Here we actually have been putting patients on at Greenwich. One of our tax dear patients.
On the Merck study, is was on there as well, so we are looking to expand these trials out to all the different care centers. Great, OK, well we’ll give Doctor Bothwell one more chance. If not, I think well will end, it has been nine years and apologized. But you know, I’ve been here 10 years and one of the first calls I got yellows from Jose Milo and who’s house are are hospital bears his name and he says Roy why do all my friends have to go to New York to go in clinical trials for prostate cancer?
And I said they will fix that.
And Dan you certainly have and you made us the destination for prostate,
bladder and other tumors.
And congratulations on your program and I think many on the.
The call here today will now perhaps have opportunities to collaborate with you 'cause and build lab to clinic studies.
So thank you all for coming to grand Rounds today.
I'll just remind everyone that on June 25th in the morning we have our annual ASCO review.
It is virtual again this year.
It’s a little shorter, but we’re going to be reviewing many topics. Dan will be there hopefully as well, and actually for a very special treat, we’re going to have Vince Devita interviewed by his daughter. Talking about the 50th anniversary of the National Cancer Act, so that’s going to be very special, so I hope to see everyone there and have a good day everyone.