WEBVTT

NOTE duration:"00:49:54.0420000"

NOTE language:en-us

NOTE Confidence: 0.78208655

00:00:00.000 --> 00:00:03.675 It's my pleasure to be host today.

NOTE Confidence: 0.78208655

00:00:03.680 --> 00:00:04.943 I'm Roy herbst.

NOTE Confidence: 0.78208655

00:00:04.943 --> 00:00:07.048 Today, we're very fortunate we

NOTE Confidence: 0.78208655

00:00:07.048 --> 00:00:09.854 have Doctor Daniel Petre lack who's

NOTE Confidence: 0.78208655

00:00:09.854 --> 00:00:12.214 professor of medical oncology and

NOTE Confidence: 0.78208655

00:00:12.214 --> 00:00:15.224 urology and the leader of our GPU program.

NOTE Confidence: 0.78208655

00:00:15.230 --> 00:00:18.102 He also of course is the leader of

NOTE Confidence: 0.78208655

00:00:18.102 --> 00:00:19.940 the signal transduction.

NOTE Confidence: 0.78208655

00:00:19.940 --> 00:00:22.936 One of those years of the signal

NOTE Confidence: 0.78208655

00:00:22.936 --> 00:00:25.498 transduction program for the care center.

NOTE Confidence: 0.78208655

00:00:25.500 --> 00:00:28.924 Dan's well known to most of us course.

NOTE Confidence: 0.78208655

00:00:28.930 --> 00:00:30.662 He spent many years.

NOTE Confidence: 0.78208655

00:00:30.662 --> 00:00:32.394 I'm at Columbia University.

NOTE Confidence: 0.78208655

00:00:32.400 --> 00:00:34.490 Before he was recruited here,

NOTE Confidence: 0.78208655

00:00:34.490 --> 00:00:36.590 now 7 plus years ago,

NOTE Confidence: 0.78208655

00:00:36.590 --> 00:00:39.936 almost eight and Dan is really, you know,

NOTE Confidence: 0.78208655

00:00:39.936 --> 00:00:42.444 been a leader in urologic cancers,

NOTE Confidence: 0.78208655

00:00:42.450 --> 00:00:44.074 bladder and prostate cancer.

NOTE Confidence: 0.78208655

00:00:44.074 --> 00:00:47.788 Just in the last year with some of his

NOTE Confidence: 0.78208655

00:00:47.788 --> 00:00:50.182 major studies working with the PROTAC

NOTE Confidence: 0.78208655

00:00:50.182 --> 00:00:52.837 with Crag Cruzen Arvinas Anthy in

NOTE Confidence: 0.78208655

00:00:52.837 --> 00:00:55.443 fortunate event and in bladder cancer.

NOTE Confidence: 0.78208655

00:00:55.443 --> 00:00:57.558 Published in the new internal

NOTE Confidence: 0.78208655

00:00:57.558 --> 00:00:59.630 medicine to name a few.

NOTE Confidence: 0.78208655

00:00:59.630 --> 00:01:01.850 He is a world leader.

NOTE Confidence: 0.78208655

00:01:01.850 --> 00:01:02.939 In this area,

NOTE Confidence: 0.78208655

00:01:02.939 --> 00:01:05.480 he's also built a team in Geo

NOTE Confidence: 0.78208655

00:01:05.567 --> 00:01:08.142 Oncology that is putting patients

NOTE Confidence: 0.78208655

00:01:08.142 --> 00:01:11.286 on protocol and raising the bar

NOTE Confidence: 0.78208655

00:01:11.286 --> 00:01:14.172 for these diseases around our care

NOTE Confidence: 0.78208655

00:01:14.172 --> 00:01:16.734 centers and around our entire

NOTE Confidence: 0.78208655

00:01:16.734 --> 00:01:20.076 network and at the main center.

NOTE Confidence: 0.78208655

00:01:20.080 --> 00:01:21.590 So then we're really excited.

NOTE Confidence: 0.78208655

00:01:21.590 --> 00:01:22.152 You know,

NOTE Confidence: 0.78208655

00:01:22.152 --> 00:01:24.119 one of the things we've been doing

NOTE Confidence: 0.78208655

00:01:24.119 --> 00:01:25.688 lately is having the different

NOTE Confidence: 0.78208655

00:01:25.688 --> 00:01:27.228 dogs presented grand rounds as

NOTE Confidence: 0.78208655

00:01:27.228 --> 00:01:29.137 a chance to sort of integrate.

NOTE Confidence: 0.78208655

00:01:29.140 --> 00:01:29.792 You know,

NOTE Confidence: 0.78208655

00:01:29.792 --> 00:01:30.770 the clinical translational

NOTE Confidence: 0.78208655

00:01:30.770 --> 00:01:32.400 program with the basic science

NOTE Confidence: 0.78208655

00:01:32.456 --> 00:01:33.914 and hopefully will have a plenty

NOTE Confidence: 0.78208655

00:01:33.914 --> 00:01:35.480 of time today for discussion.

NOTE Confidence: 0.78208655

00:01:35.480 --> 00:01:38.198 And with that I'll turn it over to you.

NOTE Confidence: 0.78208655

00:01:38.200 --> 00:01:40.307 Dan, and thank you for coming today.

NOTE Confidence: 0.87824655

00:01:41.150 --> 00:01:43.173 Thanks Roy. It's it's a pleasure being

NOTE Confidence: 0.87824655

00:01:43.173 --> 00:01:45.358 here today and thank you for inviting.

NOTE Confidence: 0.87824655

00:01:45.360 --> 00:01:47.467 You know it's actually about nine years.

NOTE Confidence: 0.87824655

00:01:47.470 --> 00:01:49.963 It's going to be September of 2012 that I

NOTE Confidence: 0.87824655

00:01:49.963 --> 00:01:52.565 came on board and it was the best decision

NOTE Confidence: 0.87824655

00:01:52.565 --> 00:01:54.998 I've ever made from a career standpoint.

NOTE Confidence: 0.87824655

00:01:55.000 --> 00:01:57.224 And I thank you and an all the

NOTE Confidence: 0.87824655

00:01:57.224 --> 00:01:59.370 leadership of the Cancer Center for

NOTE Confidence: 0.87824655

00:01:59.370 --> 00:02:01.270 being supportive over the years.

NOTE Confidence: 0.87824655

00:02:01.270 --> 00:02:03.862 And a lot of the work we're going to

NOTE Confidence: 0.87824655

00:02:03.862 --> 00:02:06.387 present here today was done by our group,

NOTE Confidence: 0.87824655

00:02:06.390 --> 00:02:07.782 including jochim, Mike Hurwitz,

NOTE Confidence: 0.87824655

00:02:07.782 --> 00:02:10.450 and but I'd like to give a first

NOTE Confidence: 0.87824655

00:02:10.450 --> 00:02:12.490 a little bit of an overview as to

NOTE Confidence: 0.87824655

00:02:12.555 --> 00:02:14.557 what is going on in prostate cancer

NOTE Confidence: 0.87824655

00:02:14.557 --> 00:02:17.648 and how do we think about it.

NOTE Confidence: 0.87824655

00:02:17.650 --> 00:02:19.696 So as we know, prostate cancer

NOTE Confidence: 0.87824655

00:02:19.696 --> 00:02:21.700 is really two different diseases.

NOTE Confidence: 0.87824655

00:02:21.700 --> 00:02:24.269 There's the disease that you die with,

NOTE Confidence: 0.87824655

00:02:24.270 --> 00:02:26.388 and this is the prostate cancer

NOTE Confidence: 0.87824655

00:02:26.388 --> 00:02:28.690 die from the Gleason 6 carcinoma,

NOTE Confidence: 0.87824655

00:02:28.690 --> 00:02:30.530 which is not none really.

NOTE Confidence: 0.87824655

00:02:30.530 --> 00:02:32.810 In some some editorials have been

NOTE Confidence: 0.87824655

00:02:32.810 --> 00:02:35.679 thought to not to be even a cancer.

NOTE Confidence: 0.87824655

00:02:35.680 --> 00:02:38.473 There was some thought about taking away

NOTE Confidence: 0.87824655

00:02:38.473 --> 00:02:40.410 from that particular classification that

NOTE Confidence: 0.87824655

00:02:40.410 --> 00:02:43.410 was in the JC a couple of years ago.

NOTE Confidence: 0.87824655

00:02:43.410 --> 00:02:44.120 That's none.

NOTE Confidence: 0.87824655

00:02:44.120 --> 00:02:46.250 That's really not going to cause

NOTE Confidence: 0.87824655

00:02:46.250 --> 00:02:47.460 a patient's demise.

NOTE Confidence: 0.87824655

00:02:47.460 --> 00:02:50.127 Even 90% chance of being biochemically free.

NOTE Confidence: 0.87824655

00:02:50.130 --> 00:02:51.790 A relapse at five years,

NOTE Confidence: 0.87824655

00:02:51.790 --> 00:02:53.450 no matter what local therapy

NOTE Confidence: 0.87824655

00:02:53.450 --> 00:02:54.778 you go forth with,

NOTE Confidence: 0.87824655

00:02:54.780 --> 00:02:57.324 we're going to focus today on

NOTE Confidence: 0.87824655

00:02:57.324 --> 00:02:59.020 the castrate resistant disease.

NOTE Confidence: 0.87824655

00:02:59.020 --> 00:03:01.750 And it's important to think about this

NOTE Confidence: 0.87824655

00:03:01.750 --> 00:03:04.350 disease in terms of clinical states.

NOTE Confidence: 0.87824655

00:03:04.350 --> 00:03:06.038 As I mentioned before,

NOTE Confidence: 0.87824655

00:03:06.038 --> 00:03:08.148 there's a clinically localized prostate

NOTE Confidence: 0.87824655

00:03:08.148 --> 00:03:10.980 cancer which can be cured with local

NOTE Confidence: 0.87824655

00:03:10.980 --> 00:03:12.544 treatment despite local treatment.

NOTE Confidence: 0.87824655

00:03:12.550 --> 00:03:14.600 No matter what you receive

NOTE Confidence: 0.87824655

00:03:14.600 --> 00:03:16.240 with its radiation therapy,

NOTE Confidence: 0.87824655

00:03:16.240 --> 00:03:19.736 hormonal therapy about one in three men in

NOTE Confidence: 0.87824655

00:03:19.736 --> 00:03:22.386 unselected cases will have a rising PSA.

NOTE Confidence: 0.87824655

00:03:22.390 --> 00:03:25.022 This can result in a biochemical relapse

NOTE Confidence: 0.87824655

00:03:25.022 --> 00:03:26.900 or eventual clinical metastases,

NOTE Confidence: 0.87824655

00:03:26.900 --> 00:03:29.636 which is the hormone sensitive state.

NOTE Confidence: 0.87824655

00:03:29.640 --> 00:03:31.370 In the non castrate disease,

NOTE Confidence: 0.87824655

00:03:31.370 --> 00:03:33.737 as we see in the upper portion of this

NOTE Confidence: 0.87824655

00:03:33.737 --> 00:03:35.745 this particular slide you also can

NOTE Confidence: 0.87824655

00:03:35.745 --> 00:03:37.916 have a rising PSA without metastatic

NOTE Confidence: 0.87824655

00:03:37.916 --> 00:03:40.448 disease and this group of patients

NOTE Confidence: 0.87824655

00:03:40.448 --> 00:03:42.776 is somewhat problematic and and when

NOTE Confidence: 0.87824655

00:03:42.776 --> 00:03:44.536 you install hormone therapy because

NOTE Confidence: 0.87824655

00:03:44.536 --> 00:03:46.775 there's some men that may never need

NOTE Confidence: 0.87824655

00:03:46.775 --> 00:03:48.687 to go on engine deprivation therapy

NOTE Confidence: 0.87824655

00:03:48.687 --> 00:03:50.937 and this of course has significant

NOTE Confidence: 0.87824655

00:03:50.937 --> 00:03:52.760 side effects including weight gain,

NOTE Confidence: 0.87824655

00:03:52.760 --> 00:03:54.484 loss of muscle mass, fatigue,

NOTE Confidence: 0.87824655

00:03:54.484 --> 00:03:55.860 loss of sexual function.

NOTE Confidence: 0.87824655

00:03:55.860 --> 00:03:58.303 So this can have a significant impact

NOTE Confidence: 0.87824655

00:03:58.303 --> 00:04:00.448 on the patient's quality of life.

NOTE Confidence: 0.87824655

00:04:00.450 --> 00:04:02.670 It's questionable whether implementation

NOTE Confidence: 0.87824655

00:04:02.670 --> 00:04:06.000 of hormone therapy at this state

NOTE Confidence: 0.87824655

00:04:06.085 --> 00:04:07.759 will improve survival.

NOTE Confidence: 0.87824655

00:04:07.760 --> 00:04:10.136 We then go on to the clinical metastases

NOTE Confidence: 0.87824655

00:04:10.136 --> 00:04:12.729 in the castrate state and there are

NOTE Confidence: 0.87824655

00:04:12.729 --> 00:04:14.659 multiple treatments that we have

NOTE Confidence: 0.87824655

00:04:14.725 --> 00:04:17.419 available and eventually we have pre

NOTE Confidence: 0.87824655

00:04:17.419 --> 00:04:19.608 chemotherapy and post chemotherapy patients.

NOTE Confidence: 0.87824655

00:04:19.608 --> 00:04:22.324 The landscape has changed and I think

NOTE Confidence: 0.87824655

00:04:22.324 --> 00:04:24.822 the important thing to remember is that

NOTE Confidence: 0.87824655

00:04:24.822 --> 00:04:26.975 this was at Doctor Charles Huggins

NOTE Confidence: 0.87824655

00:04:26.975 --> 00:04:29.150 presentation above prize in 1966.

NOTE Confidence: 0.87824655

00:04:29.150 --> 00:04:31.733 He was the person that discovered that

NOTE Confidence: 0.87824655

00:04:31.733 --> 00:04:34.040 prostate cancer is a hormone sensitive

NOTE Confidence: 0.87824655

00:04:34.040 --> 00:04:36.296 disease that if you give androgens

NOTE Confidence: 0.87824655

00:04:36.296 --> 00:04:38.487 the disease will be stimulated.

NOTE Confidence: 0.87824655

00:04:38.490 --> 00:04:40.150 But this is not curative,

NOTE Confidence: 0.87824655

00:04:40.150 --> 00:04:41.526 despite regressions of great

NOTE Confidence: 0.87824655

00:04:41.526 --> 00:04:43.590 magnitude is obvious that there are

NOTE Confidence: 0.87824655

00:04:43.647 --> 00:04:45.257 many failures of endocrine therapy

NOTE Confidence: 0.87824655

00:04:45.257 --> 00:04:46.867 to control the disease in

NOTE Confidence: 0.75882185

00:04:46.929 --> 00:04:49.141 cirrhotic that some of the greats of

NOTE Confidence: 0.75882185

00:04:49.141 --> 00:04:51.280 prostate cancer, including Doctor Huggins,

NOTE Confidence: 0.75882185

00:04:51.280 --> 00:04:54.280 actually died from Ictact disease themselves.

NOTE Confidence: 0.75882185

00:04:54.280 --> 00:04:56.560 So this is how we look

NOTE Confidence: 0.75882185

00:04:56.560 --> 00:04:58.650 at the disease in 2021.

NOTE Confidence: 0.75882185

00:04:58.650 --> 00:05:01.682 If you think back to 2004 when Docetaxel

NOTE Confidence: 0.75882185

00:05:01.682 --> 00:05:03.810 was approved was pretty simple,

NOTE Confidence: 0.75882185

00:05:03.810 --> 00:05:06.498 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

00:05:43.765 --> 00:05:46.339 and five months in this situation.

NOTE Confidence: 0.75882185

00:05:46.340 --> 00:05:47.950 So with this massive data,

NOTE Confidence: 0.75882185

00:05:47.950 --> 00:05:50.830 how do I like to think about this disease?

NOTE Confidence: 0.75882185

00:05:50.830 --> 00:05:53.014 Well, like to think of this in

NOTE Confidence: 0.75882185

00:05:53.014 --> 00:05:54.690 terms of classes of agents.

NOTE Confidence: 0.75882185

00:05:54.690 --> 00:05:56.573 We have really 4 main classes that

NOTE Confidence: 0.75882185

00:05:56.573 --> 00:05:58.890 we use from a therapeutic standpoint

NOTE Confidence: 0.75882185

00:05:58.890 --> 00:06:00.826 for castration resistant disease.

NOTE Confidence: 0.75882185

00:06:00.830 --> 00:06:01.284 Namely,

NOTE Confidence: 0.75882185

00:06:01.284 --> 00:06:03.100 immunotherapeutic agents such as

NOTE Confidence: 0.75882185

00:06:03.100 --> 00:06:06.172 Sipuleucel T Pember lose map for a

NOTE Confidence: 0.75882185

00:06:06.172 --> 00:06:08.380 small percentage of patients will be

NOTE Confidence: 0.75882185

00:06:08.380 --> 00:06:11.156 talking about a few minutes hormonal agents.

NOTE Confidence: 0.75882185

00:06:11.160 --> 00:06:12.680 Castrate resistant disease retains

NOTE Confidence: 0.75882185

00:06:12.680 --> 00:06:15.454 its hormonal axis and if you look

NOTE Confidence: 0.75882185

00:06:15.454 --> 00:06:17.170 at androgen receptor expression

NOTE Confidence: 0.75882185

00:06:17.170 --> 00:06:18.886 in specimens from patients,

NOTE Confidence: 0.75882185

00:06:18.890 --> 00:06:20.518 castration resistant prostate cancer,

NOTE Confidence: 0.75882185

00:06:20.518 --> 00:06:22.983 you'll find that about 90% still

NOTE Confidence: 0.75882185

00:06:22.983 --> 00:06:25.098 have an active androgen receptor

NOTE Confidence: 0.75882185

00:06:25.098 --> 00:06:27.618 axis and we're going to exploit

NOTE Confidence: 0.75882185

00:06:27.618 --> 00:06:29.874 that with some of these agents.

NOTE Confidence: 0.75882185

00:06:29.880 --> 00:06:30.694 In fact,

NOTE Confidence: 0.75882185

00:06:30.694 --> 00:06:33.136 it's known that some of the

NOTE Confidence: 0.75882185

00:06:33.136 --> 00:06:35.465 chemotherapeutic agents, such as docetaxel,

NOTE Confidence: 0.75882185

00:06:35.465 --> 00:06:38.495 may actually work by hormonal mechanism.

NOTE Confidence: 0.75882185

00:06:38.500 --> 00:06:40.786 What do we mean by that?

NOTE Confidence: 0.75882185

00:06:40.790 --> 00:06:41.172 Well,

NOTE Confidence: 0.75882185

00:06:41.172 --> 00:06:42.700 when you bind testosterone

NOTE Confidence: 0.75882185

00:06:42.700 --> 00:06:44.228 to the Android receptor,

NOTE Confidence: 0.75882185

00:06:44.230 --> 00:06:46.330 it has to translocate the New

NOTE Confidence: 0.75882185

00:06:46.330 --> 00:06:48.161 York nucleus and microtubules are

NOTE Confidence: 0.75882185

00:06:48.161 --> 00:06:50.369 essential to the transport of that

NOTE Confidence: 0.75882185

00:06:50.369 --> 00:06:52.364 particular complex into the nucleus

NOTE Confidence: 0.75882185

00:06:52.364 --> 00:06:54.439 I mentioned cytotoxic agents such

NOTE Confidence: 0.75882185

00:06:54.439 --> 00:06:56.071 as docetaxel cabazitaxel their

NOTE Confidence: 0.75882185

00:06:56.071 --> 00:06:58.357 isotopes that damage DNA radium 223.

NOTE Confidence: 0.75882185

00:06:58.360 --> 00:07:01.034 We're not going to get into those,

NOTE Confidence: 0.75882185

00:07:01.040 --> 00:07:03.140 but focus of investigation recently

NOTE Confidence: 0.75882185

00:07:03.140 --> 00:07:05.240 have been part inhibitors such

NOTE Confidence: 0.75882185

00:07:05.304 --> 00:07:07.518 as elaborate Kappa rib and that's

NOTE Confidence: 0.75882185

00:07:07.518 --> 00:07:09.971 appropriate for about 10 to 20% of

NOTE Confidence: 0.75882185

00:07:09.971 --> 00:07:12.095 patients with castration resistant

NOTE Confidence: 0.75882185

00:07:12.095 --> 00:07:13.157 prostate cancer.

NOTE Confidence: 0.75882185

00:07:13.160 --> 00:07:15.482 So we've been behind the long

NOTE Confidence: 0.75882185

00:07:15.482 --> 00:07:17.934 investigators as well as the breast

NOTE Confidence: 0.75882185

00:07:17.934 --> 00:07:20.009 investigators because for a long

NOTE Confidence: 0.75882185

00:07:20.009 --> 00:07:22.795 period of time we've used clinical

NOTE Confidence: 0.75882185

00:07:22.795 --> 00:07:24.256 characteristics to determine

NOTE Confidence: 0.75882185

00:07:24.256 --> 00:07:26.778 how we sequence our agents.

NOTE Confidence: 0.75882185

00:07:26.778 --> 00:07:28.482 Symptomatic versus asymptomatic,

NOTE Confidence: 0.75882185

00:07:28.482 --> 00:07:31.890 the tendency was to give hormonal

NOTE Confidence: 0.75882185

00:07:31.976 --> 00:07:34.586 therapy to those patients who had.

NOTE Confidence: 0.75882185

00:07:34.590 --> 00:07:35.918 Who are asymptomatic and

NOTE Confidence: 0.75882185

00:07:35.918 --> 00:07:37.246 safe chemotherapy for later?

NOTE Confidence: 0.75882185

00:07:37.250 --> 00:07:39.357 That may not be the right way

NOTE Confidence: 0.75882185

00:07:39.357 --> 00:07:40.676 to sequence patients visceral

NOTE Confidence: 0.75882185

00:07:40.676 --> 00:07:42.421 versus non visceral disease and

NOTE Confidence: 0.75882185

00:07:42.421 --> 00:07:44.550 then pre and post those heat.

NOTE Confidence: 0.75882185

00:07:44.550 --> 00:07:46.713 Axel was initially used as a way

NOTE Confidence: 0.75882185

00:07:46.713 --> 00:07:48.705 of approving drugs for castration

NOTE Confidence: 0.75882185

00:07:48.705 --> 00:07:50.199 resistant prostate cancer.

NOTE Confidence: 0.75882185

00:07:50.200 --> 00:07:51.127 The other issue,

NOTE Confidence: 0.75882185

00:07:51.127 --> 00:07:53.657 now which is coming into play as we've

NOTE Confidence: 0.75882185

00:07:53.657 --> 00:07:55.771 seen in breast cancer and I'm not

NOTE Confidence: 0.75882185

00:07:55.771 --> 00:07:58.337 going to go into the specifics of this,

NOTE Confidence: 0.75882185

00:07:58.340 --> 00:08:00.488 but agents which have been used

NOTE Confidence: 0.75882185

00:08:00.488 --> 00:08:01.920 traditionally to treat castration

NOTE Confidence: 0.75882185

00:08:01.980 --> 00:08:03.715 resistant disease have been moved

NOTE Confidence: 0.75882185

00:08:03.715 --> 00:08:05.450 up into the hormone sensitive

NOTE Confidence: 0.87356883

00:08:05.509 --> 00:08:07.982 state. And is actually a greater improvement

NOTE Confidence: 0.87356883

00:08:07.982 --> 00:08:10.670 in the hazard ratio when drugs such as.

NOTE Confidence: 0.8302439

00:08:16.640 --> 00:08:18.440 Hazard ratio is about .6.

NOTE Confidence: 0.8302439

00:08:18.440 --> 00:08:20.715 It's pretty significant so so that state

NOTE Confidence: 0.8302439

00:08:20.715 --> 00:08:23.494 will affect what you're going to be doing

NOTE Confidence: 0.8302439

00:08:23.494 --> 00:08:25.234 in castration resistance because the

NOTE Confidence: 0.8302439

00:08:25.296 --> 00:08:27.406 resistance patterns may be different,

NOTE Confidence: 0.8302439

00:08:27.410 --> 00:08:29.419 and we're only going to start seeing

NOTE Confidence: 0.8302439

00:08:29.419 --> 00:08:32.106 now how that may influence the treatment

NOTE Confidence: 0.8302439

00:08:32.106 --> 00:08:33.866 of castration resistant disease.

NOTE Confidence: 0.8302439

00:08:33.870 --> 00:08:36.195 Because the downstream effect only

NOTE Confidence: 0.8302439

00:08:36.195 --> 00:08:39.349 started about three to four years ago.

NOTE Confidence: 0.8302439

00:08:39.350 --> 00:08:40.806 So as I mentioned,

NOTE Confidence: 0.8302439

00:08:40.806 --> 00:08:42.626 we've been behind our colleagues

NOTE Confidence: 0.8302439

00:08:42.626 --> 00:08:45.079 in lung cancer and breast cancer

NOTE Confidence: 0.8302439

00:08:45.079 --> 00:08:47.099 and using targeted therapy and

NOTE Confidence: 0.8302439

00:08:47.172 --> 00:08:49.327 molecular markers and the three,

NOTE Confidence: 0.8302439

00:08:49.330 --> 00:08:51.724 I'm going to focus on today

NOTE Confidence: 0.8302439

00:08:51.724 --> 00:08:53.320 or the androgen receptor,

NOTE Confidence: 0.8302439

00:08:53.320 --> 00:08:55.328 those of DNA repair,

NOTE Confidence: 0.8302439

00:08:55.328 --> 00:08:57.838 and immune markers such as

NOTE Confidence: 0.8302439

00:08:57.838 --> 00:08:59.470 microcycle instability.

NOTE Confidence: 0.8302439

00:08:59.470 --> 00:09:01.710 So immune therapy is an

NOTE Confidence: 0.8302439

00:09:01.710 --> 00:09:03.054 FDA approved category.

NOTE Confidence: 0.8302439

00:09:03.060 --> 00:09:06.024 Four of the treatment of metastatic

NOTE Confidence: 0.8302439

00:09:06.024 --> 00:09:08.435 castration resistant prostate cancer and

NOTE Confidence: 0.8302439

00:09:08.435 --> 00:09:10.976 the agent that's approved in the United

NOTE Confidence: 0.8302439

00:09:10.976 --> 00:09:13.840 States is something called sipuleucel T.

NOTE Confidence: 0.8302439

00:09:13.840 --> 00:09:16.738 So this is an ecologist T cell

NOTE Confidence: 0.8302439

00:09:16.738 --> 00:09:19.040 product that's made by taking

NOTE Confidence: 0.8302439

00:09:19.040 --> 00:09:21.465 the patient's own immune cells,

NOTE Confidence: 0.8302439

00:09:21.470 --> 00:09:24.590 culturing them with a fusion protein

NOTE Confidence: 0.8302439

00:09:24.590 --> 00:09:27.150 that uses both prostatic acid

NOTE Confidence: 0.8302439

00:09:27.150 --> 00:09:29.908 phosphatase as well as a GM CSF.

NOTE Confidence: 0.8302439

00:09:29.910 --> 00:09:31.820 Fusion protein prostatic acid phosphates

NOTE Confidence: 0.8302439

00:09:31.820 --> 00:09:34.362 expressed about 90% of prostate cancer cells,

NOTE Confidence: 0.8302439

00:09:34.362 --> 00:09:37.569 so this is very specific to prostate cancer.

NOTE Confidence: 0.8302439

00:09:37.570 --> 00:09:40.244 This APC takes up this particular antigen.

NOTE Confidence: 0.8302439

00:09:40.250 --> 00:09:42.878 It's presented on the surface and

NOTE Confidence: 0.8302439

00:09:42.878 --> 00:09:46.068 you have a fully activated T cell

NOTE Confidence: 0.8302439

00:09:46.068 --> 00:09:49.197 by the time this is reinfused back

NOTE Confidence: 0.8302439

00:09:49.291 --> 00:09:52.099 to the patient three days later.

NOTE Confidence: 0.8302439

00:09:52.100 --> 00:09:54.710 So the impact trial was published

NOTE Confidence: 0.8302439

00:09:54.710 --> 00:09:57.659 in 2010 and this took patients

NOTE Confidence: 0.8302439

00:09:57.659 --> 00:10:00.454 who had had prior chemotherapy.

NOTE Confidence: 0.8302439

00:10:00.460 --> 00:10:04.646 All forms of treatment and randomize them

NOTE Confidence: 0.8302439

00:10:04.646 --> 00:10:07.960 to receive sipuleucel T or a placebo.

NOTE Confidence: 0.8302439

00:10:07.960 --> 00:10:10.634 And it was shown that there was

NOTE Confidence: 0.8302439

00:10:10.634 --> 00:10:12.313 significant improvement in overall

NOTE Confidence: 0.8302439

00:10:12.313 --> 00:10:14.618 survival in the patients who

NOTE Confidence: 0.8302439

00:10:14.618 --> 00:10:16.462 received this particular product.

NOTE Confidence: 0.8302439

00:10:16.470 --> 00:10:19.396 It was about the hazard ratio 0.775.

NOTE Confidence: 0.8302439

00:10:19.400 --> 00:10:21.808 Now what was seen in this trial

NOTE Confidence: 0.8302439

00:10:21.808 --> 00:10:24.921 and what was not seen as opposed

NOTE Confidence: 0.8302439

00:10:24.921 --> 00:10:26.917 to classic chemotherapy trials.

NOTE Confidence: 0.8302439

00:10:26.920 --> 00:10:30.245 You did not see an improvement in

NOTE Confidence: 0.8302439

00:10:30.245 --> 00:10:32.610 progression free survival and that

NOTE Confidence: 0.8302439

00:10:32.610 --> 00:10:35.599 led to a lot of skepticism initially

NOTE Confidence: 0.8302439

00:10:35.599 --> 00:10:38.846 because the PFS did not correlate with OS.

NOTE Confidence: 0.8302439

00:10:38.850 --> 00:10:39.903 Objective responses and

NOTE Confidence: 0.8302439

00:10:39.903 --> 00:10:41.307 soft tissue are infrequent.

NOTE Confidence: 0.8302439

00:10:41.310 --> 00:10:42.012 Now again,

NOTE Confidence: 0.8302439

00:10:42.012 --> 00:10:44.469 this is a select group of patients,

NOTE Confidence: 0.8302439

00:10:44.470 --> 00:10:46.570 so those patients were entered in.

NOTE Confidence: 0.8302439

00:10:46.570 --> 00:10:48.538 The study had bone only disease

NOTE Confidence: 0.8302439

00:10:48.538 --> 00:10:50.779 or a minimal lymph node disease.

NOTE Confidence: 0.8302439

00:10:50.780 --> 00:10:52.886 They did not have visceral disease.

NOTE Confidence: 0.8302439

00:10:52.890 --> 00:10:54.645 He really couldn't see whether

NOTE Confidence: 0.8302439

00:10:54.645 --> 00:10:56.049 there was a response,

NOTE Confidence: 0.8302439

00:10:56.050 --> 00:10:58.170 but generally the soft tissue

NOTE Confidence: 0.8302439

00:10:58.170 --> 00:10:59.866 disease did not respond.

NOTE Confidence: 0.8302439

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

NOTE Confidence: 0.8302439

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

NOTE Confidence: 0.8302439

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

NOTE Confidence: 0.8302439

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

NOTE Confidence: 0.8302439

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

NOTE Confidence: 0.8302439

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

NOTE Confidence: 0.8302439

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

NOTE Confidence: 0.8302439

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

NOTE Confidence: 0.8302439

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

NOTE Confidence: 0.8302439

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

NOTE Confidence: 0.8302439

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

NOTE Confidence: 0.8302439

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

NOTE Confidence: 0.8302439

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

NOTE Confidence: 0.8302439

00:11:30.142 --> 00:11:32.439 explain why this happens and Ravi Medan

NOTE Confidence: 0.8302439

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

NOTE Confidence: 0.8165383

00:12:10.468 --> 00:12:12.694 increased slope to what you've seen.

NOTE Confidence: 0.8165383

00:12:12.700 --> 00:12:14.985 When these patients were prior

NOTE Confidence: 0.8165383

00:12:14.985 --> 00:12:16.356 to their chemotherapy.

NOTE Confidence: 0.8165383

00:12:16.360 --> 00:12:18.550 With immune therapy or vaccine therapy,

NOTE Confidence: 0.8165383

00:12:18.550 --> 00:12:20.979 what you tend to see is a

NOTE Confidence: 0.8165383

00:12:20.979 --> 00:12:22.930 blunting of that PSA curve.

NOTE Confidence: 0.8165383

00:12:22.930 --> 00:12:25.120 So what you're actually doing this,

NOTE Confidence: 0.8165383

00:12:25.120 --> 00:12:26.620 but potentially missing progression

NOTE Confidence: 0.8165383

00:12:26.620 --> 00:12:28.495 events or seeing progression events

NOTE Confidence: 0.8165383

00:12:28.495 --> 00:12:30.227 and missing an overall effect.

NOTE Confidence: 0.8165383

00:12:30.230 --> 00:12:31.850 So really, the hazard ratio

NOTE Confidence: 0.8165383

00:12:31.850 --> 00:12:34.250 is what I think is important,

NOTE Confidence: 0.8165383

00:12:34.250 --> 00:12:36.440 and the overall three year survival,

NOTE Confidence: 0.8165383

00:12:36.440 --> 00:12:37.828 and unfortunately with the

NOTE Confidence: 0.8165383

00:12:37.828 --> 00:12:39.910 sipuleucel T trials they did not

NOTE Confidence: 0.8165383

00:12:39.969 --> 00:12:41.909 follow patients past three years,

NOTE Confidence: 0.8165383

00:12:41.910 --> 00:12:44.346 and I've actually been after the company

NOTE Confidence: 0.8165383

00:12:44.346 --> 00:12:47.169 to look at that particular question.

NOTE Confidence: 0.8165383

00:12:47.170 --> 00:12:49.162 To see whether there is a

NOTE Confidence: 0.8165383

00:12:49.162 --> 00:12:52.020 difference in five year, survivals.

NOTE Confidence: 0.8165383

00:12:52.020 --> 00:12:54.444 The question of molecular markers, well,

NOTE Confidence: 0.8165383

00:12:54.444 --> 00:12:57.676 we know that immune therapy with PDL one,

NOTE Confidence: 0.8165383

00:12:57.680 --> 00:12:58.892 an prostate cancer,

NOTE Confidence: 0.8165383

00:12:58.892 --> 00:13:01.720 really doesn't have a great response rate.

NOTE Confidence: 0.8165383

00:13:01.720 --> 00:13:05.356 Generally about 5 to 10% at best in terms

NOTE Confidence: 0.8165383

00:13:05.356 --> 00:13:07.780 of objective response in unselected patients.

NOTE Confidence: 0.8165383

00:13:07.780 --> 00:13:10.759 So this is a study that came out of

NOTE Confidence: 0.8165383

00:13:10.759 --> 00:13:13.430 Memorial Sloan Kettering Cancer Center,

NOTE Confidence: 0.8165383

00:13:13.430 --> 00:13:15.746 looking at 1033 patients who had

NOTE Confidence: 0.8165383

00:13:15.746 --> 00:13:17.880 MSI high in prostate cancer.

NOTE Confidence: 0.8165383

00:13:17.880 --> 00:13:21.560 It's only about a 3%.

NOTE Confidence: 0.8165383

00:13:21.560 --> 00:13:21.998 Yeah,

NOTE Confidence: 0.8165383

00:13:21.998 --> 00:13:25.064 but hit rate with that particular marker.

NOTE Confidence: 0.8165383

00:13:25.070 --> 00:13:26.806 But what's interesting is

NOTE Confidence: 0.8165383

00:13:26.806 --> 00:13:28.976 that you can see this,

NOTE Confidence: 0.8165383

00:13:28.980 --> 00:13:31.626 develop overtime that if you look at

NOTE Confidence: 0.8165383

00:13:31.626 --> 00:13:33.859 sequential specimens in patients with

NOTE Confidence: 0.8165383

00:13:33.859 --> 00:13:35.919 castrate resistant prostate cancer,

NOTE Confidence: 0.8165383

00:13:35.920 --> 00:13:38.090 you can see up regulation

NOTE Confidence: 0.8165383

00:13:38.090 --> 00:13:39.826 or development of MSI.

NOTE Confidence: 0.8165383

00:13:39.830 --> 00:13:42.441 So this is something that you really

NOTE Confidence: 0.8165383

00:13:42.441 --> 00:13:45.765 do need to check regularly and in

NOTE Confidence: 0.8165383

00:13:45.765 --> 00:13:48.420 our patients with castrate resistant

NOTE Confidence: 0.8165383

00:13:48.420 --> 00:13:51.706 disease and also seven of those 32 MSI

NOTE Confidence: 0.8165383

00:13:51.706 --> 00:13:54.191 high patients had a dream sideline

NOTE Confidence: 0.8165383

00:13:54.191 --> 00:13:55.979 mutation in Lynch's assistance.

NOTE Confidence: 0.8165383

00:13:55.980 --> 00:13:58.659 Syndrome associated gene.

NOTE Confidence: 0.8165383

00:13:58.660 --> 00:14:01.166 Does this have an effect on response

NOTE Confidence: 0.8165383

00:14:01.166 --> 00:14:02.770 to checkpoint inhibition therapy?

NOTE Confidence: 0.8165383

00:14:02.770 --> 00:14:05.770 The answer is yes. This is their series.

NOTE Confidence: 0.8165383

00:14:05.770 --> 00:14:09.127 Looking at both PDL one as well as PD.

NOTE Confidence: 0.8165383

00:14:09.130 --> 00:14:11.215 One inhibitors and castrate resistant

NOTE Confidence: 0.8165383

00:14:11.215 --> 00:14:13.792 disease and about half of patients

NOTE Confidence: 0.8165383

00:14:13.792 --> 00:14:15.877 will have objective soft tissue

NOTE Confidence: 0.8165383

00:14:15.877 --> 00:14:18.054 responses and a higher percentage

NOTE Confidence: 0.8165383

00:14:18.054 --> 00:14:20.664 of patients will have PSA declines.

NOTE Confidence: 0.8165383

00:14:20.670 --> 00:14:22.138 So in my opinion,

NOTE Confidence: 0.8165383

00:14:22.138 --> 00:14:24.340 and I think that many thought

NOTE Confidence: 0.8165383

00:14:24.419 --> 00:14:26.449 leaders feel the same way,

NOTE Confidence: 0.8165383

00:14:26.450 --> 00:14:28.095 all patients with castrate resistant

NOTE Confidence: 0.8165383

00:14:28.095 --> 00:14:30.309 prostate cancer need to be checked

NOTE Confidence: 0.8165383

00:14:30.309 --> 00:14:31.839 for microsatellite instability.

NOTE Confidence: 0.8165383

00:14:31.840 --> 00:14:34.129 Pember Lism AB is an FDA approved

NOTE Confidence: 0.8165383

00:14:34.129 --> 00:14:36.633 drug in this state of disease and

NOTE Confidence: 0.8165383

00:14:36.633 --> 00:14:39.362 this it can be administered in those

NOTE Confidence: 0.8165383

00:14:39.362 --> 00:14:42.224 patients who have that particular marker.

NOTE Confidence: 0.8165383

00:14:42.230 --> 00:14:45.094 Rushan ion has looked at CDK 12 in

NOTE Confidence: 0.8165383

00:14:45.094 --> 00:14:47.108 these patients in castrate resistant

NOTE Confidence: 0.8165383

00:14:47.108 --> 00:14:49.544 patients as well as we know,

NOTE Confidence: 0.8165383

00:14:49.550 --> 00:14:51.505 BIALLELIC mutations are formed a

NOTE Confidence: 0.8165383

00:14:51.505 --> 00:14:53.460 distinct class of prostate cancer.

NOTE Confidence: 0.8165383

00:14:53.460 --> 00:14:55.728 This leads to genomic instability as

NOTE Confidence: 0.8165383

00:14:55.728 --> 00:14:58.249 well as the development of neoantigens,

NOTE Confidence: 0.8165383

00:14:58.250 --> 00:15:01.196 and rule is also demonstrated with

NOTE Confidence: 0.8165383

00:15:01.196 --> 00:15:04.154 this particular marker that you can

NOTE Confidence: 0.8165383

00:15:04.154 --> 00:15:06.884 see increased T cell infiltration and.

NOTE Confidence: 0.8367151

00:15:06.890 --> 00:15:09.730 Also, responses in men with

NOTE Confidence: 0.8367151

00:15:09.730 --> 00:15:12.002 castrate resistant prostate cancer.

NOTE Confidence: 0.8367151

00:15:12.010 --> 00:15:14.242 So we actually LED a phase

NOTE Confidence: 0.8367151

00:15:14.242 --> 00:15:15.730 one study of atezolizumab,

NOTE Confidence: 0.8367151

00:15:15.730 --> 00:15:17.206 an castrate resistant disease.

NOTE Confidence: 0.8367151

00:15:17.206 --> 00:15:19.051 This was published in clinical

NOTE Confidence: 0.8367151

00:15:19.051 --> 00:15:20.939 Cancer Research earlier this year.

NOTE Confidence: 0.8367151

00:15:20.940 --> 00:15:24.288 Joe Kim and I were coauthors on this patient.

NOTE Confidence: 0.8367151

00:15:24.290 --> 00:15:26.145 This particular study and we

NOTE Confidence: 0.8367151

00:15:26.145 --> 00:15:27.629 had two different cohorts.

NOTE Confidence: 0.8367151

00:15:27.630 --> 00:15:30.606 In initial phase, one cohort of 10 patients,

NOTE Confidence: 0.8367151

00:15:30.610 --> 00:15:33.207 and then a 15 patient expansion cohort.

NOTE Confidence: 0.8367151

00:15:33.210 --> 00:15:35.070 As we can see here,

NOTE Confidence: 0.8367151

00:15:35.070 --> 00:15:37.303 the response rates with a Tesla some

NOTE Confidence: 0.8367151

00:15:37.303 --> 00:15:39.170 AB were somewhat disappointing.

NOTE Confidence: 0.8367151

00:15:39.170 --> 00:15:39.944 About 50%.

NOTE Confidence: 0.8367151

00:15:39.944 --> 00:15:42.266 These are patients who had multiple.

NOTE Confidence: 0.8367151

00:15:42.270 --> 00:15:44.650 Prior chemotherapies or immunol hormonal

NOTE Confidence: 0.8367151

00:15:44.650 --> 00:15:47.950 therapies and we did see a fairly

NOTE Confidence: 0.8367151

00:15:47.950 --> 00:15:50.476 good meeting survival of 14.7 months,

NOTE Confidence: 0.8367151

00:15:50.480 --> 00:15:54.016 but this is unselected and there were two

NOTE Confidence: 0.8367151

00:15:54.016 --> 00:15:56.409 partial responses by resist criteria.

NOTE Confidence: 0.8367151

00:15:56.410 --> 00:16:00.988 Overall now we tried to look for.

NOTE Confidence: 0.8367151

00:16:00.990 --> 00:16:02.379 Molecular characterization that

NOTE Confidence: 0.8367151

00:16:02.379 --> 00:16:05.157 may lead us to understand better

NOTE Confidence: 0.8367151

00:16:05.157 --> 00:16:07.389 why these patients responded.

NOTE Confidence: 0.8367151

00:16:07.390 --> 00:16:10.470 We saw some higher levels of CD8

NOTE Confidence: 0.8367151

00:16:10.470 --> 00:16:13.289 in these patients after treatment.

NOTE Confidence: 0.8367151

00:16:13.290 --> 00:16:16.242 We did not see any significant

NOTE Confidence: 0.8367151

00:16:16.242 --> 00:16:17.718 PDL one expression,

NOTE Confidence: 0.8367151

00:16:17.720 --> 00:16:20.666 nor did we find microsatellite instability.

NOTE Confidence: 0.8367151

00:16:20.670 --> 00:16:24.114 And this is one of our responders

NOTE Confidence: 0.8367151

00:16:24.114 --> 00:16:25.590 who is microsatellites.

NOTE Confidence: 0.8367151

00:16:25.590 --> 00:16:28.674 Table had really not a particularly

NOTE Confidence: 0.8367151

00:16:28.674 --> 00:16:31.340 higher level 22 mutation rates.

NOTE Confidence: 0.8367151

00:16:31.340 --> 00:16:33.644 But he did have a mutation

NOTE Confidence: 0.8367151

00:16:33.644 --> 00:16:35.720 in ATM which you know.

NOTE Confidence: 0.8367151

00:16:35.720 --> 00:16:37.328 Again, there been others.

NOTE Confidence: 0.8367151

00:16:37.328 --> 00:16:39.338 Some others have correlated responses

NOTE Confidence: 0.8367151

00:16:39.338 --> 00:16:41.289 with these DNA repair enzymes,

NOTE Confidence: 0.8367151

00:16:41.290 --> 00:16:44.377 but this was really 2 number too

NOTE Confidence: 0.8367151

00:16:44.377 --> 00:16:47.908 small to make any great conclusions.

NOTE Confidence: 0.8367151

00:16:47.910 --> 00:16:50.052 So where are we moving and

NOTE Confidence: 0.8367151

00:16:50.052 --> 00:16:50.766 immunotherapy yellow?

NOTE Confidence: 0.8367151

00:16:50.770 --> 00:16:52.852 And what's or some of the

NOTE Confidence: 0.8367151

00:16:52.852 --> 00:16:55.070 trials that are open right now?

NOTE Confidence: 0.8367151

00:16:55.070 --> 00:16:57.218 Well, we've been looking at it,

NOTE Confidence: 0.8367151

00:16:57.220 --> 00:16:59.236 Ralph, up with a bio excel and

NOTE Confidence: 0.8367151

00:16:59.236 --> 00:17:01.510 this is in resistant patients,

NOTE Confidence: 0.8367151

00:17:01.510 --> 00:17:02.240 both newer,

NOTE Confidence: 0.8367151

00:17:02.240 --> 00:17:04.430 castrate resistant as well as small

NOTE Confidence: 0.8367151

00:17:04.430 --> 00:17:06.168 cell carcinoma of the prostate.

NOTE Confidence: 0.8367151

00:17:06.170 --> 00:17:08.342 Looking at DP 8-9 inhibition with

NOTE Confidence: 0.8367151

00:17:08.342 --> 00:17:10.517 the Excel 701201 combined with the

NOTE Confidence: 0.8367151

00:17:10.517 --> 00:17:12.503 volume in this trial is ongoing

NOTE Confidence: 0.8367151

00:17:12.503 --> 00:17:14.400 and occurring patients right now.

NOTE Confidence: 0.8367151

00:17:14.400 --> 00:17:16.976 Joe Kim in the Phase one group.

NOTE Confidence: 0.8367151

00:17:16.980 --> 00:17:19.416 Is looking at a novel combination of

NOTE Confidence: 0.8367151

00:17:19.416 --> 00:17:21.342 ateez allusion mab, along with cables,

NOTE Confidence: 0.8367151

00:17:21.342 --> 00:17:23.895 and which is a TKI which is which

NOTE Confidence: 0.8367151

00:17:23.895 --> 00:17:26.025 actually was originally looked in.

NOTE Confidence: 0.8367151

00:17:26.030 --> 00:17:29.606 Prostate cancer number of years ago.

NOTE Confidence: 0.8367151

00:17:29.610 --> 00:17:31.958 But really, a failed phase, three studies.

NOTE Confidence: 0.8367151

00:17:31.958 --> 00:17:33.628 And as we saw before,

NOTE Confidence: 0.8367151

00:17:33.630 --> 00:17:35.975 it is losing members and 8% response

NOTE Confidence: 0.8367151

00:17:35.975 --> 00:17:38.320 rate cables got a 5% response rate.

NOTE Confidence: 0.8367151

00:17:38.320 --> 00:17:40.665 You put the two of them together.

NOTE Confidence: 0.8367151

00:17:40.670 --> 00:17:42.704 They've got a 30% response rate

NOTE Confidence: 0.8367151

00:17:42.704 --> 00:17:45.018 and Joe is working in the phase.

NOTE Confidence: 0.8367151

00:17:45.020 --> 00:17:48.156 One group is also designing a phase one

NOTE Confidence: 0.8367151

00:17:48.156 --> 00:17:51.228 study to look at biological markers.

NOTE Confidence: 0.8367151

00:17:51.230 --> 00:17:53.210 Small select group of patients

NOTE Confidence: 0.8367151

00:17:53.210 --> 00:17:54.398 with this combination,

NOTE Confidence: 0.8367151

00:17:54.400 --> 00:17:56.782 we've completed a vaccine study of

NOTE Confidence: 0.8367151

00:17:56.782 --> 00:17:58.750 APSA construct with Tremolux Moab.

NOTE Confidence: 0.8367151

00:17:58.750 --> 00:18:01.126 The interesting thing about this trial,

NOTE Confidence: 0.8367151

00:18:01.130 --> 00:18:03.110 it was just presented yesterday.

NOTE Confidence: 0.8367151

00:18:03.110 --> 00:18:05.658 Tasco is that we saw responses in

NOTE Confidence: 0.8367151

00:18:05.658 --> 00:18:07.701 patients who are hormone sensitive

NOTE Confidence: 0.8367151

00:18:07.701 --> 00:18:09.449 with a rising PSA.

NOTE Confidence: 0.8367151

00:18:09.450 --> 00:18:11.766 Really didn't see any really significant

NOTE Confidence: 0.8367151

00:18:11.766 --> 00:18:13.800 activity in castrate resistant disease,

NOTE Confidence: 0.8367151

00:18:13.800 --> 00:18:16.768 but unless we did have a couple of

NOTE Confidence: 0.8367151

00:18:16.768 --> 00:18:18.924 responses were still looking some

NOTE Confidence: 0.8367151

00:18:18.924 --> 00:18:21.600 of the biologic korelitz and then.

NOTE Confidence: 0.8367151

00:18:21.600 --> 00:18:22.002 Finally.

NOTE Confidence: 0.8367151

00:18:22.002 --> 00:18:24.414 We completed accrual in a phase

NOTE Confidence: 0.8367151

00:18:24.414 --> 00:18:26.991 three trial of Docetaxel plus and

NOTE Confidence: 0.8367151

00:18:26.991 --> 00:18:29.146 minus pember Lism AB International

NOTE Confidence: 0.8367151

00:18:29.146 --> 00:18:31.668 Pi on that and hopefully we'll

NOTE Confidence: 0.8367151

00:18:31.668 --> 00:18:34.038 see a positive result of that

NOTE Confidence: 0.7329831

00:18:34.040 --> 00:18:35.860 particular study.

NOTE Confidence: 0.7329831

00:18:35.860 --> 00:18:38.786 Now I mentioned before that in the

NOTE Confidence: 0.7329831

00:18:38.786 --> 00:18:40.914 castration resistant state you still

NOTE Confidence: 0.7329831

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

NOTE Confidence: 0.7329831

00:19:18.810 --> 00:19:20.410 pathway of androgen synthesis.

NOTE Confidence: 0.7329831

00:19:20.410 --> 00:19:22.010 There are also alternative

NOTE Confidence: 0.7329831

00:19:22.010 --> 00:19:22.810 splicing mechanisms.

NOTE Confidence: 0.7329831

00:19:22.810 --> 00:19:24.810 There's aberrant function these mutations,

NOTE Confidence: 0.7329831

00:19:24.810 --> 00:19:27.610 which will give you gain of function,

NOTE Confidence: 0.7329831

00:19:27.610 --> 00:19:31.210 which will will talk about in a few moments.

NOTE Confidence: 0.7329831

00:19:31.210 --> 00:19:33.175 But all these particular pathways

NOTE Confidence: 0.7329831

00:19:33.175 --> 00:19:35.631 can lead to deregulation of the

NOTE Confidence: 0.7329831

00:19:35.631 --> 00:19:37.726 androgen receptor despite the fact.

NOTE Confidence: 0.7329831

00:19:37.730 --> 00:19:40.508 That there are serum levels of

NOTE Confidence: 0.7329831

00:19:40.508 --> 00:19:42.360 testosterone that are castrated.

NOTE Confidence: 0.7329831

00:19:42.360 --> 00:19:44.656 So one way that we can overcome

NOTE Confidence: 0.7329831

00:19:44.656 --> 00:19:45.640 this of course,

NOTE Confidence: 0.7329831

00:19:45.640 --> 00:19:47.384 is shutting down testosterone

NOTE Confidence: 0.7329831

00:19:47.384 --> 00:19:48.256 synthesis completely.

NOTE Confidence: 0.7329831

00:19:48.260 --> 00:19:49.445 Testosterone is predominately

NOTE Confidence: 0.7329831

00:19:49.445 --> 00:19:51.420 made with from the testicles,

NOTE Confidence: 0.7329831

00:19:51.420 --> 00:19:53.400 but as I mentioned before,

NOTE Confidence: 0.7329831

00:19:53.400 --> 00:19:55.896 the prostate cancer cells can make

NOTE Confidence: 0.7329831

00:19:55.896 --> 00:19:58.722 their own testosterone as well as the

NOTE Confidence: 0.7329831

00:19:58.722 --> 00:20:01.254 adrenals that is actually about 20% of

NOTE Confidence: 0.7329831

00:20:01.254 --> 00:20:03.732 all the testosterone is created so you

NOTE Confidence: 0.7329831

00:20:03.732 --> 00:20:06.428 drink or text to peripheral tissues.

NOTE Confidence: 0.7329831

00:20:06.430 --> 00:20:08.920 You can shut down these particular

NOTE Confidence: 0.7329831

00:20:08.920 --> 00:20:11.168 pathways by 1720 lyase inhibition

NOTE Confidence: 0.7329831

00:20:11.168 --> 00:20:13.718 with a drug called abiraterone.

NOTE Confidence: 0.7329831

00:20:13.720 --> 00:20:15.680 And this is the chemical

NOTE Confidence: 0.7329831

00:20:15.680 --> 00:20:17.236 structure of Apparate, Rhone.

NOTE Confidence: 0.7329831

00:20:17.236 --> 00:20:19.492 There's a second way of blocking

NOTE Confidence: 0.7329831

00:20:19.492 --> 00:20:21.190 the Android receptor pathway,

NOTE Confidence: 0.7329831

00:20:21.190 --> 00:20:22.542 which is FDA approved.

NOTE Confidence: 0.7329831

00:20:22.542 --> 00:20:24.232 And that's using anti androgens

NOTE Confidence: 0.7329831

00:20:24.232 --> 00:20:25.951 which directly antagonized the

NOTE Confidence: 0.7329831

00:20:25.951 --> 00:20:27.711 receptors enzalutamide was rationally

NOTE Confidence: 0.7329831

00:20:27.711 --> 00:20:30.255 designed from a series of different

NOTE Confidence: 0.7329831

00:20:30.255 --> 00:20:32.200 compounds that was selected for

NOTE Confidence: 0.7329831

00:20:32.200 --> 00:20:33.372 androgen receptor antagonism.

NOTE Confidence: 0.7329831

00:20:33.372 --> 00:20:35.724 The interesting thing about this drug,

NOTE Confidence: 0.7329831

00:20:35.730 --> 00:20:37.640 although overtime it's been shown

NOTE Confidence: 0.7329831

00:20:37.640 --> 00:20:40.425 that we see very very we see

NOTE Confidence: 0.7329831

00:20:40.425 --> 00:20:42.435 this occasionally is that there's

NOTE Confidence: 0.7329831

00:20:42.435 --> 00:20:43.641 no known agonist.

NOTE Confidence: 0.7329831

00:20:43.650 --> 00:20:45.636 Activity see this occasionally with patients.

NOTE Confidence: 0.7329831

00:20:45.640 --> 00:20:47.596 There is some of these anti

NOTE Confidence: 0.7329831

00:20:47.596 --> 00:20:49.290 androgens when you stop them.

NOTE Confidence: 0.7329831

00:20:49.290 --> 00:20:51.236 The PSA actually goes down and we

NOTE Confidence: 0.7329831

00:20:51.236 --> 00:20:53.699 still have not been able to correctly

NOTE Confidence: 0.7329831

00:20:53.699 --> 00:20:55.263 explain that particular effect.

NOTE Confidence: 0.7329831

00:20:55.270 --> 00:20:56.930 So you can decrease testosterone

NOTE Confidence: 0.7329831

00:20:56.930 --> 00:20:58.590 levels and block the receptors.

NOTE Confidence: 0.7329831

00:20:58.590 --> 00:21:00.711 Now the fact is these both of

NOTE Confidence: 0.7329831

00:21:00.711 --> 00:21:02.569 these drugs are FDA approved.

NOTE Confidence: 0.7329831

00:21:02.570 --> 00:21:04.165 They both improve survival again

NOTE Confidence: 0.7329831

00:21:04.165 --> 00:21:06.230 by about three to four months.

NOTE Confidence: 0.7329831

00:21:06.230 --> 00:21:07.938 As we've seen before.

NOTE Confidence: 0.7329831

00:21:07.938 --> 00:21:10.073 Do we sequence them because

NOTE Confidence: 0.7329831

00:21:10.073 --> 00:21:12.677 these drugs in terms of toxicity,

NOTE Confidence: 0.7329831

00:21:12.680 --> 00:21:15.291 seemed to be less toxic than giving

NOTE Confidence: 0.7329831

00:21:15.291 --> 00:21:17.189 attack scene such as kabasi,

NOTE Confidence: 0.7329831

00:21:17.190 --> 00:21:18.570 Taxol, docetaxel, unfortunately?

NOTE Confidence: 0.7329831

00:21:18.570 --> 00:21:20.870 This cross resistance between these

NOTE Confidence: 0.7329831

00:21:20.870 --> 00:21:23.837 agents PSA responses are generally 10 to 20%,

NOTE Confidence: 0.7329831

00:21:23.840 --> 00:21:26.395 and you see a progression free survival

NOTE Confidence: 0.7329831

00:21:26.395 --> 00:21:28.578 of about three to four months.

NOTE Confidence: 0.7329831

00:21:28.580 --> 00:21:31.154 If you sequence Abby after ends

NOTE Confidence: 0.7329831

00:21:31.154 --> 00:21:32.870 or ends after Abby.

NOTE Confidence: 0.7329831

00:21:32.870 --> 00:21:35.210 And also refining to that,

NOTE Confidence: 0.7329831

00:21:35.210 --> 00:21:38.465 taxing's are less effective and vice versa.

NOTE Confidence: 0.7329831

00:21:38.470 --> 00:21:41.278 These drugs are also less effective.

NOTE Confidence: 0.7329831

00:21:41.280 --> 00:21:43.788 Act after Taxing's and there may

NOTE Confidence: 0.7329831

00:21:43.788 --> 00:21:46.410 be some slight cross resistance.

NOTE Confidence: 0.7329831

00:21:46.410 --> 00:21:49.224 So kimchi at University of Vancouver

NOTE Confidence: 0.7329831

00:21:49.224 --> 00:21:51.550 is actually summarized this data,

NOTE Confidence: 0.7329831

00:21:51.550 --> 00:21:54.609 and if we look across the board

NOTE Confidence: 0.7329831

00:21:54.609 --> 00:21:55.920 as I mentioned

NOTE Confidence: 0.820178

00:21:56.024 --> 00:21:59.252 before, a best we see a survival

NOTE Confidence: 0.820178

00:21:59.252 --> 00:22:01.820 of 8.7 about 12 months.

NOTE Confidence: 0.820178

00:22:01.820 --> 00:22:05.510 If you give these drugs sequentially.

NOTE Confidence: 0.820178

00:22:05.510 --> 00:22:08.326 And PSA decline rates of 20 to 30%,

NOTE Confidence: 0.820178

00:22:08.330 --> 00:22:10.095 whereas the single agent drugs

NOTE Confidence: 0.820178

00:22:10.095 --> 00:22:12.184 are about 50 to 60% overall.

NOTE Confidence: 0.820178

00:22:12.184 --> 00:22:14.776 So how do we look at this in

NOTE Confidence: 0.820178

00:22:14.776 --> 00:22:17.069 terms of resistance resistance?

NOTE Confidence: 0.820178

00:22:17.070 --> 00:22:18.909 I mentioned before,

NOTE Confidence: 0.820178

00:22:18.909 --> 00:22:21.361 you could have upregulation

NOTE Confidence: 0.820178

00:22:21.361 --> 00:22:23.200 of different pathways.

NOTE Confidence: 0.820178

00:22:23.200 --> 00:22:25.450 And particularly CYP 17 you could

NOTE Confidence: 0.820178

00:22:25.450 --> 00:22:27.640 also see these splice variants.

NOTE Confidence: 0.820178

00:22:27.640 --> 00:22:29.896 You can see induction of glucocorticoid

NOTE Confidence: 0.820178

00:22:29.896 --> 00:22:32.358 expression that also may be related

NOTE Confidence: 0.820178

00:22:32.358 --> 00:22:33.699 to enzalutamide resistance,

NOTE Confidence: 0.820178

00:22:33.700 --> 00:22:36.046 so they again are multiple pathways

NOTE Confidence: 0.820178

00:22:36.046 --> 00:22:38.550 that we can go forth with.

NOTE Confidence: 0.820178

00:22:38.550 --> 00:22:41.578 One is error V7.

NOTE Confidence: 0.820178

00:22:41.580 --> 00:22:44.156 Play RV 7 is is a truncated

NOTE Confidence: 0.820178

00:22:44.156 --> 00:22:46.929 version of the androgen receptor.

NOTE Confidence: 0.820178

00:22:46.930 --> 00:22:48.710 The Android receptor has

NOTE Confidence: 0.820178

00:22:48.710 --> 00:22:50.045 three different components.

NOTE Confidence: 0.820178

00:22:50.050 --> 00:22:53.179 One is the the DNA binding region,

NOTE Confidence: 0.820178

00:22:53.180 --> 00:22:56.724 the other one is the liggen binding region

NOTE Confidence: 0.820178

00:22:56.724 --> 00:23:00.305 and then the other is the hinge region.

NOTE Confidence: 0.820178

00:23:00.310 --> 00:23:02.907 So the login biting region is deleted

NOTE Confidence: 0.820178

00:23:02.907 --> 00:23:06.821 in a RV 7 so this can be constituency

NOTE Confidence: 0.820178

00:23:06.821 --> 00:23:09.326 activated and then 'cause activation

NOTE Confidence: 0.820178

00:23:09.326 --> 00:23:12.346 of the androgen receptor pathway.

NOTE Confidence: 0.820178

00:23:12.350 --> 00:23:14.062 It has to dimerize.

NOTE Confidence: 0.820178

00:23:14.062 --> 00:23:15.774 So that's actually important

NOTE Confidence: 0.820178

00:23:15.774 --> 00:23:17.630 fact as we see here.

NOTE Confidence: 0.820178

00:23:17.630 --> 00:23:19.142 From this particular slide,

NOTE Confidence: 0.820178

00:23:19.142 --> 00:23:21.410 this is from my colleague Daniel

NOTE Confidence: 0.820178

00:23:21.480 --> 00:23:23.308 Interactice at Johns Hopkins.

NOTE Confidence: 0.820178

00:23:23.310 --> 00:23:25.404 If you look at those patients

NOTE Confidence: 0.820178

00:23:25.404 --> 00:23:27.818 who are AR V7 negative versus

NOTE Confidence: 0.820178

00:23:27.818 --> 00:23:30.620 those who are very 7 positive,

NOTE Confidence: 0.820178

00:23:30.620 --> 00:23:32.858 they have a better progression free

NOTE Confidence: 0.820178

00:23:32.858 --> 00:23:35.301 survival when you're treating these drugs

NOTE Confidence: 0.820178

00:23:35.301 --> 00:23:37.516 in patients with abiraterone enzalutamide,

NOTE Confidence: 0.820178

00:23:37.520 --> 00:23:39.550 you also better PSA responses.

NOTE Confidence: 0.820178

00:23:39.550 --> 00:23:42.469 So if you make a RV 7.

NOTE Confidence: 0.820178

00:23:42.470 --> 00:23:44.375 You're less likely to respond

NOTE Confidence: 0.820178

00:23:44.375 --> 00:23:46.280 to these particular drugs now.

NOTE Confidence: 0.820178

00:23:46.280 --> 00:23:48.947 Taxing's are a little bit more responsive,

NOTE Confidence: 0.820178

00:23:48.950 --> 00:23:50.855 but the response rate with

NOTE Confidence: 0.820178

00:23:50.855 --> 00:23:52.760 taxes or not as good.

NOTE Confidence: 0.820178

00:23:52.760 --> 00:23:53.522 But again,

NOTE Confidence: 0.820178

00:23:53.522 --> 00:23:56.189 you see a difference between the RV,

NOTE Confidence: 0.820178

00:23:56.190 --> 00:23:58.090 7 positives and the negatives,

NOTE Confidence: 0.820178

00:23:58.090 --> 00:24:00.659 but overall taxes do have a better

NOTE Confidence: 0.820178

00:24:00.659 --> 00:24:03.038 response in those who are positive,

NOTE Confidence: 0.820178

00:24:03.040 --> 00:24:05.870 so this data was performed

NOTE Confidence: 0.820178

00:24:05.870 --> 00:24:08.700 in patients with CTC's so.

NOTE Confidence: 0.820178

00:24:08.700 --> 00:24:11.496 This is associated with primary resistance.

NOTE Confidence: 0.820178

00:24:11.500 --> 00:24:13.835 The positive patients may still

NOTE Confidence: 0.820178

00:24:13.835 --> 00:24:15.703 become sensitive to taxanes,

NOTE Confidence: 0.820178

00:24:15.710 --> 00:24:17.574 but in positive men,

NOTE Confidence: 0.820178

00:24:17.574 --> 00:24:19.904 taxanes may be more effective.

NOTE Confidence: 0.820178

00:24:19.910 --> 00:24:23.216 Acacius and there may be comparative

NOTE Confidence: 0.820178

00:24:23.216 --> 00:24:26.484 efficacy with targeted agents in the

NOTE Confidence: 0.820178

00:24:26.484 --> 00:24:28.929 negative patients compared to the.

NOTE Confidence: 0.820178

00:24:28.930 --> 00:24:31.336 The the these next generation ages,

NOTE Confidence: 0.820178

00:24:31.340 --> 00:24:32.759 such tabron enzalutamide.

NOTE Confidence: 0.820178

00:24:32.759 --> 00:24:37.229 So this leads us to a trial called card.

NOTE Confidence: 0.820178

00:24:37.230 --> 00:24:39.530 And this is important political

NOTE Confidence: 0.820178

00:24:39.530 --> 00:24:41.830 implications to our patients because

NOTE Confidence: 0.820178

00:24:41.905 --> 00:24:44.271 What Car did was it took patients

NOTE Confidence: 0.820178

00:24:44.271 --> 00:24:46.190 who had received abiraterone or

NOTE Confidence: 0.820178

00:24:46.190 --> 00:24:48.680 enzalutamide for one year or less,

NOTE Confidence: 0.820178

00:24:48.680 --> 00:24:51.140 then went on to receive docetaxel.

NOTE Confidence: 0.820178

00:24:51.140 --> 00:24:52.343 And of course,

NOTE Confidence: 0.820178

00:24:52.343 --> 00:24:54.348 the dilemma that physicians have

NOTE Confidence: 0.820178

00:24:54.348 --> 00:24:57.137 in the situation is whether you

NOTE Confidence: 0.820178

00:24:57.137 --> 00:24:59.517 treat with an alternative anti

NOTE Confidence: 0.820178

00:24:59.517 --> 00:25:02.220 androgen or to give a chemotherapy

NOTE Confidence: 0.820178

00:25:02.220 --> 00:25:03.940 agent such as cabazitaxel.

NOTE Confidence: 0.820178

00:25:03.940 --> 00:25:04.858 And this trial,

NOTE Confidence: 0.820178

00:25:04.858 --> 00:25:05.470 I think,

NOTE Confidence: 0.820178

00:25:05.470 --> 00:25:07.258 lends credence to the fact that

NOTE Confidence: 0.820178

00:25:07.258 --> 00:25:09.132 these AR V7 mutants may actually

NOTE Confidence: 0.820178

00:25:09.132 --> 00:25:10.974 persist for a period of time,

NOTE Confidence: 0.820178

00:25:10.980 --> 00:25:13.031 because if you give a second androgen

NOTE Confidence: 0.820178

00:25:13.031 --> 00:25:14.958 signaling agent so the opposite agent,

NOTE Confidence: 0.820178

00:25:14.960 --> 00:25:16.490 if they've got Abby first,

NOTE Confidence: 0.820178

00:25:16.490 --> 00:25:17.710 then they get enzalutamide.

NOTE Confidence: 0.820178

00:25:17.710 --> 00:25:18.930 If they get enzalutamide,

NOTE Confidence: 0.820178

00:25:18.930 --> 00:25:21.990 then they get abiraterone.

NOTE Confidence: 0.820178

00:25:21.990 --> 00:25:24.120 You have a better survival with

NOTE Confidence: 0.820178

00:25:24.120 --> 00:25:26.609 cabazitaxel then with the secondary agent,

NOTE Confidence: 0.820178

00:25:26.610 --> 00:25:28.968 and that's both in terms of

NOTE Confidence: 0.820178

00:25:28.968 --> 00:25:30.540 both progression free as

NOTE Confidence: 0.82304096

00:25:30.618 --> 00:25:32.886 oh as well as overall survival

NOTE Confidence: 0.82304096

00:25:32.886 --> 00:25:35.079 at the hazard ratio of 0.64.

NOTE Confidence: 0.82304096

00:25:35.080 --> 00:25:37.558 So in sequence we tend to use

NOTE Confidence: 0.82304096

00:25:37.558 --> 00:25:39.700 chemotherapy earlier in these patients.

NOTE Confidence: 0.82304096

00:25:39.700 --> 00:25:42.780 So what are we working on at Yale?

NOTE Confidence: 0.82304096

00:25:42.780 --> 00:25:45.332 That may be a way of moving forward

NOTE Confidence: 0.82304096

00:25:45.332 --> 00:25:47.400 with this particular pathway?

NOTE Confidence: 0.82304096

00:25:47.400 --> 00:25:49.330 Well, number of years ago?

NOTE Confidence: 0.82304096

00:25:49.330 --> 00:25:50.515 Roy, you know,

NOTE Confidence: 0.82304096

00:25:50.515 --> 00:25:52.885 one of the things I think.

NOTE Confidence: 0.82304096

00:25:52.890 --> 00:25:54.330 You need about Yale,

NOTE Confidence: 0.82304096

00:25:54.330 --> 00:25:57.090 and I think the pandemic is really.

NOTE Confidence: 0.82304096

00:25:57.090 --> 00:25:58.777 As really hurt is this seminar we

NOTE Confidence: 0.82304096

00:25:58.777 --> 00:26:00.657 used to have on Tuesday afternoons

NOTE Confidence: 0.82304096

00:26:00.657 --> 00:26:02.125 between the chemistry department

NOTE Confidence: 0.82304096

00:26:02.125 --> 00:26:04.329 and the Medical oncology department.

NOTE Confidence: 0.82304096

00:26:04.330 --> 00:26:06.796 Roy was really instrumental in getting

NOTE Confidence: 0.82304096

00:26:06.796 --> 00:26:08.998 this going forward forward and Craig

NOTE Confidence: 0.82304096

00:26:08.998 --> 00:26:11.353 Crews came up to me at one of these

NOTE Confidence: 0.82304096

00:26:11.353 --> 00:26:13.565 meetings and said you have a need

NOTE Confidence: 0.82304096

00:26:13.565 --> 00:26:15.572 for Brooke drugs and prostate cancer,

NOTE Confidence: 0.82304096

00:26:15.572 --> 00:26:17.999 and it's absolutely he's would you want

NOTE Confidence: 0.82304096

00:26:17.999 --> 00:26:20.120 to go forth with another hormonal age.

NOTE Confidence: 0.82304096

00:26:20.120 --> 00:26:21.436 And I said absolutely,

NOTE Confidence: 0.82304096

00:26:21.436 --> 00:26:23.410 there's room for that because there's

NOTE Confidence: 0.82304096

00:26:23.468 --> 00:26:25.058 a mechanistic approach to it,

NOTE Confidence: 0.82304096

00:26:25.060 --> 00:26:27.482 and it turns out that the company

NOTE Confidence: 0.82304096

00:26:27.482 --> 00:26:29.339 that Craig previously had founded.

NOTE Confidence: 0.82304096

00:26:29.340 --> 00:26:31.944 CEO had died from metastatic prostate cancer,

NOTE Confidence: 0.82304096

00:26:31.950 --> 00:26:34.326 so he was on a mission to find

NOTE Confidence: 0.82304096

00:26:34.326 --> 00:26:36.683 other agents and this was really

NOTE Confidence: 0.82304096

00:26:36.683 --> 00:26:38.371 the perfect collaboration between

NOTE Confidence: 0.82304096

00:26:38.371 --> 00:26:40.530 a bench and Ben's bedside.

NOTE Confidence: 0.82304096

00:26:40.530 --> 00:26:42.768 So this is a novel drug.

NOTE Confidence: 0.82304096

00:26:42.770 --> 00:26:45.434 This is a RV110 and what's

NOTE Confidence: 0.82304096

00:26:45.434 --> 00:26:47.210 the science behind this?

NOTE Confidence: 0.82304096

00:26:47.210 --> 00:26:50.346 Well, we're trying to degrade the proteins,

NOTE Confidence: 0.82304096

00:26:50.350 --> 00:26:52.590 so there's a natural pathway.

NOTE Confidence: 0.82304096

00:26:52.590 --> 00:26:54.096 The proteasome pathway,

NOTE Confidence: 0.82304096

00:26:54.096 --> 00:26:56.606 which we basically can degrade

NOTE Confidence: 0.82304096

00:26:56.606 --> 00:26:59.310 proteins with a bug within our body.

NOTE Confidence: 0.82304096

00:26:59.310 --> 00:27:01.908 Soap Protex are ways of basically

NOTE Confidence: 0.82304096

00:27:01.908 --> 00:27:04.230 accelerating this ubiquitin based pathway,

NOTE Confidence: 0.82304096

00:27:04.230 --> 00:27:07.366 so you have a disease causing protein.

NOTE Confidence: 0.82304096

00:27:07.370 --> 00:27:10.506 E3 ubiquitin ligase will bind to that.

NOTE Confidence: 0.82304096

00:27:10.510 --> 00:27:13.018 The Pro tech will actually accelerate

NOTE Confidence: 0.82304096

00:27:13.018 --> 00:27:15.335 that and then this induces

NOTE Confidence: 0.82304096

00:27:15.335 --> 00:27:18.140 ubiquitination of the target protein.

NOTE Confidence: 0.82304096

00:27:18.140 --> 00:27:18.784 And this,

NOTE Confidence: 0.82304096

00:27:18.784 --> 00:27:20.716 I think the neat thing about

NOTE Confidence: 0.82304096

00:27:20.716 --> 00:27:22.569 this drug is it's recycled.

NOTE Confidence: 0.82304096

00:27:22.570 --> 00:27:26.280 You can have as many as 400.

NOTE Confidence: 0.82304096

00:27:26.280 --> 00:27:28.040 Throat androgen receptors proteins

NOTE Confidence: 0.82304096

00:27:28.040 --> 00:27:31.800 that can be taken out by this pro tech.

NOTE Confidence: 0.82304096

00:27:31.800 --> 00:27:35.128 In a given cell and then it basically

NOTE Confidence: 0.82304096

00:27:35.128 --> 00:27:37.709 is destroyed by the protein cell.

NOTE Confidence: 0.82304096

00:27:37.710 --> 00:27:40.657 So why is this called a dumbbell?

NOTE Confidence: 0.82304096

00:27:40.660 --> 00:27:43.614 Well, this is the shape of it.

NOTE Confidence: 0.82304096

00:27:43.620 --> 00:27:46.483 There's a protein login domain which is

NOTE Confidence: 0.82304096

00:27:46.483 --> 00:27:49.099 the warhead targets a specific protein.

NOTE Confidence: 0.82304096

00:27:49.100 --> 00:27:51.866 It's linked to the ligase Lagann

NOTE Confidence: 0.82304096

00:27:51.866 --> 00:27:54.220 which recruits the E3 ubiquitin

NOTE Confidence: 0.82304096

00:27:54.220 --> 00:27:57.146 ligase and so all three of these

NOTE Confidence: 0.82304096

00:27:57.146 --> 00:28:00.468 play a role in protein degradation.

NOTE Confidence: 0.82304096

00:28:00.470 --> 00:28:03.221 So how is this related to prostate

NOTE Confidence: 0.82304096

00:28:03.221 --> 00:28:04.730 cancer with a RV?

NOTE Confidence: 0.82304096

00:28:04.730 --> 00:28:07.439 110 is a pro tech that targets

NOTE Confidence: 0.82304096

00:28:07.439 --> 00:28:08.600 the engine receptor.

NOTE Confidence: 0.82304096

00:28:08.600 --> 00:28:10.530 So as we mentioned before,

NOTE Confidence: 0.82304096

00:28:10.530 --> 00:28:12.680 you can have amplification and

NOTE Confidence: 0.82304096

00:28:12.680 --> 00:28:15.293 receptor mutations and this this was

NOTE Confidence: 0.82304096

00:28:15.293 --> 00:28:17.627 developed both in an in androgen

NOTE Confidence: 0.82304096

00:28:17.627 --> 00:28:19.660 insulin resistant as well as

NOTE Confidence: 0.82304096

00:28:19.660 --> 00:28:20.848 sensitive cell lines.

NOTE Confidence: 0.82304096

00:28:20.850 --> 00:28:23.724 So there are variety of different

NOTE Confidence: 0.82304096

00:28:23.724 --> 00:28:26.673 mutations that this pro tech will

NOTE Confidence: 0.82304096

00:28:26.673 --> 00:28:29.028 degrade the T878H75Y the F877L

NOTE Confidence: 0.82304096

00:28:29.028 --> 00:28:31.600 the MV895 point mutations but not

NOTE Confidence: 0.82304096

00:28:31.600 --> 00:28:33.385 L 2702 an AR V7.

NOTE Confidence: 0.82304096

00:28:33.390 --> 00:28:36.398 So does that mean that it's not going

NOTE Confidence: 0.82304096

00:28:36.398 --> 00:28:39.670 to work in these particular subtypes?

NOTE Confidence: 0.82304096

00:28:39.670 --> 00:28:42.590 The answer is no because if you look

NOTE Confidence: 0.82304096

00:28:42.590 --> 00:28:45.067 at Doctor Interactice paper carefully

NOTE Confidence: 0.82304096

00:28:45.067 --> 00:28:48.397 for New England Journal of Medicine

NOTE Confidence: 0.82304096

00:28:48.397 --> 00:28:51.577 you'll find that in addition to having.

NOTE Confidence: 0.82304096

00:28:51.580 --> 00:28:52.705 The air B7.

NOTE Confidence: 0.82304096

00:28:52.705 --> 00:28:53.830 This usually amplification

NOTE Confidence: 0.82304096

00:28:53.830 --> 00:28:55.330 of and wild type

NOTE Confidence: 0.81504536

00:28:55.399 --> 00:28:57.479 and receptor which could be

NOTE Confidence: 0.81504536

00:28:57.479 --> 00:28:59.559 affected by the different Protex.

NOTE Confidence: 0.81504536

00:28:59.560 --> 00:29:02.423 So this may also affect amplification of

NOTE Confidence: 0.81504536

00:29:02.423 --> 00:29:05.550 the wild type receptor as we see here.

NOTE Confidence: 0.81504536

00:29:05.550 --> 00:29:08.110 It's going to degrade 90% of

NOTE Confidence: 0.81504536

00:29:08.110 --> 00:29:10.960 the engine receptor in vitro.

NOTE Confidence: 0.81504536

00:29:10.960 --> 00:29:13.984 So two years ago we opened up the phase

NOTE Confidence: 0.81504536

00:29:13.984 --> 00:29:17.573 one study that looked at AR V110IN men

NOTE Confidence: 0.81504536

00:29:17.573 --> 00:29:20.270 with castrate resistant prostate cancer.

NOTE Confidence: 0.81504536

00:29:20.270 --> 00:29:22.802 They had to have at least

NOTE Confidence: 0.81504536

00:29:22.802 --> 00:29:24.068 two prior therapies.

NOTE Confidence: 0.81504536

00:29:24.070 --> 00:29:26.446 We did not basically eliminate those

NOTE Confidence: 0.81504536

00:29:26.446 --> 00:29:28.730 patients who had extensive treatment.

NOTE Confidence: 0.81504536

00:29:28.730 --> 00:29:31.268 We had required that they have

NOTE Confidence: 0.81504536

00:29:31.268 --> 00:29:32.960 either abiraterone or enzalutamide.

NOTE Confidence: 0.8112661

00:29:35.080 --> 00:29:37.516 It took us a little while to

NOTE Confidence: 0.8112661

00:29:37.516 --> 00:29:40.348 get to the 140 milligram dose,

NOTE Confidence: 0.8112661

00:29:40.350 --> 00:29:42.989 which is what was important in the

NOTE Confidence: 0.8112661

00:29:42.989 --> 00:29:44.800 laboratory to achieve activity.

NOTE Confidence: 0.8112661

00:29:44.800 --> 00:29:47.635 So this is the minimal efficacious dose.

NOTE Confidence: 0.8112661

00:29:47.640 --> 00:29:50.744 As I mentioned before on the day 15

NOTE Confidence: 0.8112661

00:29:50.744 --> 00:29:54.273 AUC and Cmax this was achieved at

NOTE Confidence: 0.8112661

00:29:54.273 --> 00:29:56.933 140 milligrams or greater orally.

NOTE Confidence: 0.8112661

00:29:56.940 --> 00:29:58.750 So here's some some evidence

NOTE Confidence: 0.8112661

00:29:58.750 --> 00:30:01.120 that we are hitting the target.

NOTE Confidence: 0.8112661

00:30:01.120 --> 00:30:03.598 This is a patient of ours that

NOTE Confidence: 0.8112661

00:30:03.598 --> 00:30:06.035 was treated with ARVs 110 and we

NOTE Confidence: 0.8112661

00:30:06.035 --> 00:30:08.621 have both a baseline and it big

NOTE Confidence: 0.8112661

00:30:08.621 --> 00:30:10.881 posttreatment biopsy that shows

NOTE Confidence: 0.8112661

00:30:10.881 --> 00:30:13.706 downregulation of the Android receptor.

NOTE Confidence: 0.8112661

00:30:13.710 --> 00:30:15.054 Remember these are heavily

NOTE Confidence: 0.8112661

00:30:15.054 --> 00:30:15.726 pretreated patients.

NOTE Confidence: 0.8112661

00:30:15.730 --> 00:30:18.089 This is our presentation from last year.

NOTE Confidence: 0.8112661

00:30:18.090 --> 00:30:20.365 We see that there is one patient

NOTE Confidence: 0.8112661

00:30:20.365 --> 00:30:23.153 out at 35 weeks of duration of

NOTE Confidence: 0.8112661

00:30:23.153 --> 00:30:25.751 treatment and we did see responses.

NOTE Confidence: 0.8112661

00:30:25.760 --> 00:30:28.898 As measured by a PSA decline,

NOTE Confidence: 0.8112661

00:30:28.900 --> 00:30:32.098 we saw two patients with PSA

NOTE Confidence: 0.8112661

00:30:32.098 --> 00:30:35.320 declines of at least 50% an.

NOTE Confidence: 0.8112661

00:30:35.320 --> 00:30:37.270 Lo and behold,

NOTE Confidence: 0.8112661

00:30:37.270 --> 00:30:40.520 these patients had degradable engine

NOTE Confidence: 0.8112661

00:30:40.520 --> 00:30:43.609 receptor mutations T87A at 875Y.

NOTE Confidence: 0.8112661

00:30:43.610 --> 00:30:46.158 And we see here that that one

NOTE Confidence: 0.8112661

00:30:46.158 --> 00:30:48.709 patient with the RV 7 did have

NOTE Confidence: 0.8112661

00:30:48.709 --> 00:30:50.424 a very minor PSA decline,

NOTE Confidence: 0.8112661

00:30:50.430 --> 00:30:52.936 but he also had a concomitant mutation.

NOTE Confidence: 0.8112661

00:30:52.940 --> 00:30:54.596 So are responding.

NOTE Confidence: 0.8112661

00:30:54.596 --> 00:30:57.356 Patient here at Yale head.

NOTE Confidence: 0.8112661

00:30:57.360 --> 00:30:58.320 Multiple treatments,

NOTE Confidence: 0.8112661

00:30:58.320 --> 00:30:59.280 including docetaxel,

NOTE Confidence: 0.8112661

00:30:59.280 --> 00:30:59.760 abiraterone,

NOTE Confidence: 0.8112661

00:30:59.760 --> 00:31:01.425 radium and enzalutamide,

NOTE Confidence: 0.8112661

00:31:01.425 --> 00:31:04.755 he had eight eight 7597-A mutation

NOTE Confidence: 0.8112661

00:31:04.755 --> 00:31:07.915 and he had a 74% PSA reduction after

NOTE Confidence: 0.8112661

00:31:07.915 --> 00:31:10.340 his treatment was administered and

NOTE Confidence: 0.8112661

00:31:10.340 --> 00:31:13.168 his time of the presentation is.

NOTE Confidence: 0.8112661

00:31:13.170 --> 00:31:16.038 Duration of response was 30 weeks.

NOTE Confidence: 0.8112661

00:31:16.040 --> 00:31:18.430 This is a patient from

NOTE Confidence: 0.8112661

00:31:18.430 --> 00:31:20.342 Nick Vogelsang at Nevada,

NOTE Confidence: 0.8112661

00:31:20.350 --> 00:31:25.390 also with a very with the same mutation

NOTE Confidence: 0.8112661

00:31:25.390 --> 00:31:29.407 pattern showing a PSA reduction of 97%.

NOTE Confidence: 0.8112661

00:31:29.410 --> 00:31:30.718 And soft tissue responses.

NOTE Confidence: 0.8112661

00:31:30.718 --> 00:31:32.680 So where are we going with

NOTE Confidence: 0.8112661

00:31:32.751 --> 00:31:34.359 this particular treatment?

NOTE Confidence: 0.8112661

00:31:34.360 --> 00:31:35.776 We still have two.

NOTE Confidence: 0.8112661

00:31:35.776 --> 00:31:37.900 We have a phase two trial

NOTE Confidence: 0.8112661

00:31:37.985 --> 00:31:40.080 with two open sub cohorts.

NOTE Confidence: 0.8112661

00:31:40.080 --> 00:31:42.252 Those patients who harbored a RT

NOTE Confidence: 0.8112661

00:31:42.252 --> 00:31:44.953 7-8 or 75 mutation were taking up

NOTE Confidence: 0.8112661

00:31:44.953 --> 00:31:47.317 to 20 patients were still accruing,

NOTE Confidence: 0.8112661

00:31:47.320 --> 00:31:49.516 and then those patients who received

NOTE Confidence: 0.8112661

00:31:49.516 --> 00:31:51.439 a prior second generation and

NOTE Confidence: 0.8112661

00:31:51.439 --> 00:31:53.409 androgens and no prior chemotherapy.

NOTE Confidence: 0.8112661

00:31:53.410 --> 00:31:54.172 The subgroup,

NOTE Confidence: 0.8112661

00:31:54.172 --> 00:31:57.220 one subgroup force are now close to accrual.

NOTE Confidence: 0.8112661

00:31:57.220 --> 00:31:59.985 At least there an accrual hold it.

NOTE Confidence: 0.8112661

00:31:59.990 --> 00:32:01.097 This particular point,

NOTE Confidence: 0.8112661

00:32:01.097 --> 00:32:02.942 so hopefully will open those

NOTE Confidence: 0.8112661

00:32:02.942 --> 00:32:04.510 in the near future,

NOTE Confidence: 0.8112661

00:32:04.510 --> 00:32:07.222 and I'd like to know the last minutes

NOTE Confidence: 0.8112661

00:32:07.222 --> 00:32:10.106 of this talk talk about some of Jochems

NOTE Confidence: 0.8112661

00:32:10.106 --> 00:32:13.189 work in in with with PARP inhibitors.

NOTE Confidence: 0.8112661

00:32:13.190 --> 00:32:14.342 As we know,

NOTE Confidence: 0.8112661

00:32:14.342 --> 00:32:16.262 DNA repair mutations are present

NOTE Confidence: 0.8112661

00:32:16.262 --> 00:32:18.461 in about 10% of patients with

NOTE Confidence: 0.8112661

00:32:18.461 --> 00:32:19.969 castrate resistant prostate cancer.

NOTE Confidence: 0.8112661

00:32:19.970 --> 00:32:21.101 These are predominantly

NOTE Confidence: 0.8112661

00:32:21.101 --> 00:32:22.986 bracket one and bracket twos,

NOTE Confidence: 0.8112661

00:32:22.990 --> 00:32:26.838 but we see a variety of other other

NOTE Confidence: 0.8112661

00:32:26.838 --> 00:32:29.539 mutations such as ATM check too.

NOTE Confidence: 0.8112661

00:32:29.540 --> 00:32:31.824 Powerbi Tunan rad 51.

NOTE Confidence: 0.8112661

00:32:31.824 --> 00:32:33.537 As we know,

NOTE Confidence: 0.8112661

00:32:33.540 --> 00:32:36.048 Prop inhibitors work by the mechanism

NOTE Confidence: 0.8112661

00:32:36.048 --> 00:32:38.533 of synthetic lethality where this is

NOTE Confidence: 0.8112661

00:32:38.533 --> 00:32:40.765 involved in single stranded DNA repair,

NOTE Confidence: 0.8112661

00:32:40.770 --> 00:32:43.680 whereas other agents are involved in

NOTE Confidence: 0.8112661

00:32:43.680 --> 00:32:47.029 double stranded breaks and the two of

NOTE Confidence: 0.8112661

00:32:47.029 --> 00:32:49.693 them combined together can cause synergy.

NOTE Confidence: 0.8112661

00:32:49.700 --> 00:32:52.170 So elaborate has been evaluated

NOTE Confidence: 0.8112661

00:32:52.170 --> 00:32:54.146 in castration resistant prostate

NOTE Confidence: 0.8112661

00:32:54.146 --> 00:32:56.177 cancer in a phase two trial.

NOTE Confidence: 0.8112661

00:32:56.180 --> 00:32:58.604 This was published in the journal

NOTE Confidence: 0.8112661

00:32:58.604 --> 00:33:01.360 by Joe Johann de Bono's group,

NOTE Confidence: 0.8112661

00:33:01.360 --> 00:33:02.224 49 patients.

NOTE Confidence: 0.8112661

00:33:02.224 --> 00:33:02.656 Overall,

NOTE Confidence: 0.8112661

00:33:02.656 --> 00:33:05.252 the response rate was 32.7% when

NOTE Confidence: 0.8112661

00:33:05.252 --> 00:33:06.980 they went back retrospectively

NOTE Confidence: 0.8112661

00:33:06.980 --> 00:33:08.708 looked at genomic analysis.

NOTE Confidence: 0.8112661

00:33:08.710 --> 00:33:10.925 They found that third of

NOTE Confidence: 0.8112661

00:33:10.925 --> 00:33:13.140 patients with mutations in DNA

NOTE Confidence: 0.8081576

00:33:13.227 --> 00:33:14.759 repair 2/3 did not.

NOTE Confidence: 0.8081576

00:33:14.760 --> 00:33:17.567 14 of those 16 patients with the

NOTE Confidence: 0.8081576

00:33:17.567 --> 00:33:19.610 DNA repair mutations responded.

NOTE Confidence: 0.8081576

00:33:19.610 --> 00:33:21.794 Where is only two patients who did not

NOTE Confidence: 0.8081576

00:33:21.794 --> 00:33:23.888 have that repair mutation responded.

NOTE Confidence: 0.8081576

00:33:23.890 --> 00:33:26.308 This led to the profound trial

NOTE Confidence: 0.8081576

00:33:26.308 --> 00:33:28.300 which looked at aerolab rib.

NOTE Confidence: 0.8081576

00:33:28.300 --> 00:33:30.586 And two different cohorts of patients,

NOTE Confidence: 0.8081576

00:33:30.590 --> 00:33:32.876 both those who are a bracket,

NOTE Confidence: 0.8081576

00:33:32.880 --> 00:33:35.178 one bracket, two or ATM positive,

NOTE Confidence: 0.8081576

00:33:35.180 --> 00:33:38.617 or other DNA repair mutations in these

NOTE Confidence: 0.8081576

00:33:38.617 --> 00:33:41.362 patients were randomized to receive either

NOTE Confidence: 0.8081576

00:33:41.362 --> 00:33:44.850 a lap RIV or physicians choice of therapy.

NOTE Confidence: 0.8081576

00:33:44.850 --> 00:33:47.125 The trial did meet its primary endpoint,

NOTE Confidence: 0.8081576

00:33:47.130 --> 00:33:48.426 which was radio graphic

NOTE Confidence: 0.8081576

00:33:48.426 --> 00:33:49.398 progression free survival.

NOTE Confidence: 0.8081576

00:33:49.400 --> 00:33:51.675 This was in the bracket one bracket,

NOTE Confidence: 0.8081576

00:33:51.680 --> 00:33:52.708 two or ATM cohorts.

NOTE Confidence: 0.8081576

00:33:52.708 --> 00:33:55.132 There was about a four month difference in

NOTE Confidence: 0.8081576

00:33:55.132 --> 00:33:57.197 radio graphic progression free survival,

NOTE Confidence: 0.8081576

00:33:57.200 --> 00:33:59.150 and when you look at all

NOTE Confidence: 0.8081576

00:33:59.150 --> 00:34:00.450 cohorts of DNA repair,

NOTE Confidence: 0.8081576

00:34:00.450 --> 00:34:02.725 there was about a two month difference,

NOTE Confidence: 0.8081576

00:34:02.730 --> 00:34:06.066 but the hazard ratio was 0.49.

NOTE Confidence: 0.8081576

00:34:06.070 --> 00:34:07.578 Now this I think,

NOTE Confidence: 0.8081576

00:34:07.578 --> 00:34:10.710 is one of the important slides from this.

NOTE Confidence: 0.8081576

00:34:10.710 --> 00:34:12.612 This paper we see that those

NOTE Confidence: 0.8081576

00:34:12.612 --> 00:34:14.361 patients who have ATM mutations

NOTE Confidence: 0.8081576

00:34:14.361 --> 00:34:16.421 really don't have a particularly

NOTE Confidence: 0.8081576

00:34:16.421 --> 00:34:18.840 great response to PARP inhibitors.

NOTE Confidence: 0.8081576

00:34:18.840 --> 00:34:19.612 In fact,

NOTE Confidence: 0.8081576

00:34:19.612 --> 00:34:22.314 their hazard ratio is one for death,

NOTE Confidence: 0.8081576

00:34:22.320 --> 00:34:24.205 and that's that's really different

NOTE Confidence: 0.8081576

00:34:24.205 --> 00:34:26.969 than what we see with the bracket.

NOTE Confidence: 0.8081576

00:34:26.970 --> 00:34:29.762 One and bracket twos and the PR2 3RA's

NOTE Confidence: 0.8081576

00:34:29.762 --> 00:34:32.000 actually do worse with partition.

NOTE Confidence: 0.8081576

00:34:32.000 --> 00:34:34.709 This is the survival from the trial.

NOTE Confidence: 0.8081576

00:34:34.710 --> 00:34:37.140 We see that there is a.

NOTE Confidence: 0.8081576

00:34:37.140 --> 00:34:38.948 Improvement in overall survival

NOTE Confidence: 0.8081576

00:34:38.948 --> 00:34:41.660 has ratio 0.64 and big difference

NOTE Confidence: 0.8081576

00:34:41.737 --> 00:34:43.986 in response rate 33% versus 2.3%.

NOTE Confidence: 0.8081576

00:34:43.986 --> 00:34:46.554 So this drug is FDA approved.

NOTE Confidence: 0.8081576

00:34:46.560 --> 00:34:49.368 The second FDA approved drug is recap rib

NOTE Confidence: 0.8081576

00:34:49.368 --> 00:34:52.977 in a slightly different group of patients,

NOTE Confidence: 0.8081576

00:34:52.980 --> 00:34:55.010 whereas patients in the profound

NOTE Confidence: 0.8081576

00:34:55.010 --> 00:34:57.040 trial were either refractory to

NOTE Confidence: 0.8081576

00:34:57.112 --> 00:34:59.397 chemotherapy or two next generation.

NOTE Confidence: 0.8081576

00:34:59.400 --> 00:35:00.684 And are androids.

NOTE Confidence: 0.8081576

00:35:00.684 --> 00:35:03.680 This study was a phase two trial,

NOTE Confidence: 0.8081576

00:35:03.680 --> 00:35:06.482 not a phase three trial that

NOTE Confidence: 0.8081576

00:35:06.482 --> 00:35:08.350 led to accelerated approval.

NOTE Confidence: 0.8081576

00:35:08.350 --> 00:35:10.835 In those patients who had

NOTE Confidence: 0.8081576

00:35:10.835 --> 00:35:12.326 DNA repair mutations,

NOTE Confidence: 0.8081576

00:35:12.330 --> 00:35:16.460 who would be progressed after either a

NOTE Confidence: 0.8081576

00:35:16.460 --> 00:35:20.228 Apparate Ronan's little mind or apalutamide?

NOTE Confidence: 0.8081576

00:35:20.230 --> 00:35:23.058 As we see from this slide here,

NOTE Confidence: 0.8081576

00:35:23.060 --> 00:35:25.130 we predominantly have those patients

NOTE Confidence: 0.8081576

00:35:25.130 --> 00:35:27.910 who have bracket one bracket choose an.

NOTE Confidence: 0.8081576

00:35:27.910 --> 00:35:28.716 Not surprisingly,

NOTE Confidence: 0.8081576

00:35:28.716 --> 00:35:31.537 a similar response rate with CAP ribbon.

NOTE Confidence: 0.8081576

00:35:31.540 --> 00:35:33.964 The Bracco Bracco one bracket use

NOTE Confidence: 0.8081576

00:35:33.964 --> 00:35:36.390 44% but again the same pattern.

NOTE Confidence: 0.8081576

00:35:36.390 --> 00:35:38.856 No real difference in no objective

NOTE Confidence: 0.8081576

00:35:38.856 --> 00:35:40.922 responses in those patients have

NOTE Confidence: 0.8081576

00:35:40.922 --> 00:35:43.379 ATM mutations and the same as far

NOTE Confidence: 0.8081576

00:35:43.379 --> 00:35:45.170 as biochemical responses concerned

NOTE Confidence: 0.8081576

00:35:45.170 --> 00:35:46.892 51% bracket one bracket,

NOTE Confidence: 0.8081576

00:35:46.892 --> 00:35:50.004 two said at least a 50% PSA decline.

NOTE Confidence: 0.8081576

00:35:50.004 --> 00:35:51.030 Where is none,

NOTE Confidence: 0.8081576

00:35:51.030 --> 00:35:53.938 had declines in ATM.

NOTE Confidence: 0.8081576

00:35:53.940 --> 00:35:56.540 So in this time just click add a

NOTE Confidence: 0.8081576

00:35:56.540 --> 00:35:58.948 little bit and think about what

NOTE Confidence: 0.8081576

00:35:58.948 --> 00:36:01.048 we've been thinking about it.

NOTE Confidence: 0.8081576

00:36:01.050 --> 00:36:03.578 Yale in terms of strategy as far as

NOTE Confidence: 0.8081576

00:36:03.578 --> 00:36:06.329 how we can potentially improve the OR

NOTE Confidence: 0.8081576

00:36:06.329 --> 00:36:09.649 at least expand the use of part numbers.

NOTE Confidence: 0.8081576

00:36:09.650 --> 00:36:10.030 Well,

NOTE Confidence: 0.8081576

00:36:10.030 --> 00:36:11.930 there are variety of different

NOTE Confidence: 0.8081576

00:36:11.930 --> 00:36:13.868 agents that will synergize with

NOTE Confidence: 0.8081576

00:36:13.868 --> 00:36:15.628 PARPAN inhibitors in in vitro.

NOTE Confidence: 0.8081576

00:36:15.630 --> 00:36:17.500 These include Becca Mecca, hitters,

NOTE Confidence: 0.8081576

00:36:17.500 --> 00:36:19.750 bet inhibitors, PR, 3 kinase inhibitors,

NOTE Confidence: 0.8081576

00:36:19.750 --> 00:36:20.872 androgen receptor pathway.

NOTE Confidence: 0.8081576

00:36:20.872 --> 00:36:24.248 That is, we're planning a trial of of.

NOTE Confidence: 0.8081576

00:36:24.250 --> 00:36:27.292 Everyone 10 plus abiraterone but also

NOTE Confidence: 0.8081576

00:36:27.292 --> 00:36:29.699 antiangiogenic agents and Joakim is

NOTE Confidence: 0.8081576

00:36:29.699 --> 00:36:32.131 and and his also looked at the trial

NOTE Confidence: 0.8081576

00:36:32.131 --> 00:36:35.010 of this of elaborate combined with

NOTE Confidence: 0.8081576

00:36:35.010 --> 00:36:37.510 Sadir nib Ancaster resistant disease,

NOTE Confidence: 0.75593275

00:36:37.510 --> 00:36:40.604 as we see here, it's an inducer

NOTE Confidence: 0.75593275

00:36:40.604 --> 00:36:42.368 of hypoxemia, sadir treatment.

NOTE Confidence: 0.75593275

00:36:42.368 --> 00:36:44.563 Patient treated cells do have

NOTE Confidence: 0.75593275

00:36:44.563 --> 00:36:46.789 more hypoxi than the vehicle,

NOTE Confidence: 0.75593275

00:36:46.790 --> 00:36:50.366 and we know that elaborate works in about

NOTE Confidence: 0.75593275

00:36:50.366 --> 00:36:54.260 10 to 20% of all prostate cancer patients.

NOTE Confidence: 0.75593275

00:36:54.260 --> 00:36:56.920 And from the data from Doctor Bender's

NOTE Confidence: 0.75593275

00:36:56.920 --> 00:36:58.923 laboratory in preclinical data showing

NOTE Confidence: 0.75593275

00:36:58.923 --> 00:37:00.918 that angiogenesis may be involved,

NOTE Confidence: 0.75593275

00:37:00.920 --> 00:37:03.368 the combination of elaborate and steered

NOTE Confidence: 0.75593275

00:37:03.368 --> 00:37:05.793 have seemed to be moving illogical

NOTE Confidence: 0.75593275

00:37:05.793 --> 00:37:08.665 and come forth with this was for a

NOTE Confidence: 0.75593275

00:37:08.737 --> 00:37:11.101 presentation at ASCO early ask AGERE

NOTE Confidence: 0.75593275

00:37:11.101 --> 00:37:13.925 earlier in the year looking at a

NOTE Confidence: 0.75593275

00:37:13.925 --> 00:37:16.000 randomized phase two trial comparing

NOTE Confidence: 0.75593275

00:37:16.000 --> 00:37:18.582 elaborate plus a deer nib to steerman

NOTE Confidence: 0.75593275

00:37:18.582 --> 00:37:20.920 along these were non selected patients.

NOTE Confidence: 0.75593275

00:37:20.920 --> 00:37:23.664 We wanted to look at this in

NOTE Confidence: 0.75593275

00:37:23.664 --> 00:37:25.922 retrospective pet fashion. This is.

NOTE Confidence: 0.75593275

00:37:25.922 --> 00:37:28.627 Was spearheaded by Joseph Kim.

NOTE Confidence: 0.75593275

00:37:28.630 --> 00:37:31.066 Overall, we enrolled 90 patients nationally,

NOTE Confidence: 0.75593275

00:37:31.070 --> 00:37:32.750 45 in the combination.

NOTE Confidence: 0.75593275

00:37:32.750 --> 00:37:36.360 Each of the each different arms of the study.

NOTE Confidence: 0.75593275

00:37:36.360 --> 00:37:38.802 These were patients with a median

NOTE Confidence: 0.75593275

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 --> 00:37:59.620 overall 31% had some form of

NOTE Confidence: 0.75593275

00:37:59.620 --> 00:38:00.970 DNA repair mutations,

NOTE Confidence: 0.75593275

00:38:00.970 --> 00:38:04.378 either bracket one or bracket 2.

NOTE Confidence: 0.75593275

00:38:04.380 --> 00:38:06.431 The trial did meet its primary endpoint

NOTE Confidence: 0.75593275

00:38:06.431 --> 00:38:07.930 in unselected patients progression.

NOTE Confidence: 0.75593275

00:38:07.930 --> 00:38:10.296 Free survival was better in the combination

NOTE Confidence: 0.75593275

00:38:10.296 --> 00:38:13.099 arm than it was in the single agent arm,

NOTE Confidence: 0.75593275

00:38:13.100 --> 00:38:15.354 but we started looking at the data.

NOTE Confidence: 0.75593275

00:38:15.360 --> 00:38:18.013 We see some patterns which I think

NOTE Confidence: 0.75593275

00:38:18.013 --> 00:38:21.479 could lead us to where we can go

NOTE Confidence: 0.75593275

00:38:21.479 --> 00:38:23.729 forward with this particular approach.

NOTE Confidence: 0.75593275

00:38:23.730 --> 00:38:26.229 We don't see really an improvement in

NOTE Confidence: 0.75593275

00:38:26.229 --> 00:38:28.009 progression free survival in those

NOTE Confidence: 0.75593275

00:38:28.009 --> 00:38:29.629 patients who are HR proficient.

NOTE Confidence: 0.75593275

00:38:29.630 --> 00:38:32.406 We do see that in the deficient ones,

NOTE Confidence: 0.75593275

00:38:32.410 --> 00:38:34.867 be interesting to see whether it does

NOTE Confidence: 0.75593275

00:38:34.867 --> 00:38:37.603 seem to be somewhat better than what

NOTE Confidence: 0.75593275

00:38:37.603 --> 00:38:40.530 we see with the POP inhibitor alone.

NOTE Confidence: 0.75593275

00:38:40.530 --> 00:38:43.815 But there does seem to be in a very,

NOTE Confidence: 0.75593275

00:38:43.820 --> 00:38:45.640 very small number of patients.

NOTE Confidence: 0.75593275

00:38:45.640 --> 00:38:47.470 Some response in those patients

NOTE Confidence: 0.75593275

00:38:47.470 --> 00:38:49.720 at least improvement in PFS in

NOTE Confidence: 0.75593275

00:38:49.720 --> 00:38:51.480 those patients or ATM positive.

NOTE Confidence: 0.75593275

00:38:51.480 --> 00:38:54.028 So this may be lead for future

NOTE Confidence: 0.75593275

00:38:54.028 --> 00:38:55.914 investigation as one would expect

NOTE Confidence: 0.75593275

00:38:55.914 --> 00:38:58.413 in such a small trial like this,

NOTE Confidence: 0.75593275

00:38:58.420 --> 00:39:01.340 you're not going to see a survival benefit,

NOTE Confidence: 0.75593275

00:39:01.340 --> 00:39:03.160 but there is, you know.

NOTE Confidence: 0.75593275

00:39:03.160 --> 00:39:03.874 But again,

NOTE Confidence: 0.75593275

00:39:03.874 --> 00:39:06.016 that's something we need to look

NOTE Confidence: 0.75593275

00:39:06.016 --> 00:39:08.583 at in the properly powered study

NOTE Confidence: 0.75593275

00:39:08.583 --> 00:39:10.808 so it really does summarize.

NOTE Confidence: 0.75593275

00:39:10.810 --> 00:39:13.302 We see a difference in the combination

NOTE Confidence: 0.75593275

00:39:13.302 --> 00:39:15.410 therapy in terms of progression,

NOTE Confidence: 0.75593275

00:39:15.410 --> 00:39:16.978 free survival and exploratory

NOTE Confidence: 0.75593275

00:39:16.978 --> 00:39:19.802 analysis is seeing that that in these

NOTE Confidence: 0.75593275

00:39:19.802 --> 00:39:21.827 particular subgroups there does seem

NOTE Confidence: 0.75593275

00:39:21.827 --> 00:39:24.218 to be an improvement in our PFS,

NOTE Confidence: 0.75593275

00:39:24.220 --> 00:39:26.873 so this is something I think this

NOTE Confidence: 0.75593275

00:39:26.873 --> 00:39:29.190 speaks plourd further in this disease,

NOTE Confidence: 0.75593275

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

NOTE Confidence: 0.75593275

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

NOTE Confidence: 0.75593275

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

NOTE Confidence: 0.75593275

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

NOTE Confidence: 0.75593275

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

NOTE Confidence: 0.75593275

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

NOTE Confidence: 0.75593275

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

NOTE Confidence: 0.75593275

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

NOTE Confidence: 0.75593275

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

NOTE Confidence: 0.75593275

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

NOTE Confidence: 0.75593275

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

NOTE Confidence: 0.75593275

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

NOTE Confidence: 0.75593275

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

NOTE Confidence: 0.75593275

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

NOTE Confidence: 0.75593275

00:39:56.984 --> 00:39:58.720 with castration resistant disease

NOTE Confidence: 0.810913899999999

00:39:58.784 --> 00:40:01.232 and we're looking forward to going

NOTE Confidence: 0.810913899999999

00:40:01.232 --> 00:40:03.621 forth with novel combinations to expand

NOTE Confidence: 0.810913899999999

00:40:03.621 --> 00:40:06.029 the spectrum of patients who may be

NOTE Confidence: 0.810913899999999

00:40:06.029 --> 00:40:09.920 eligible to receive part. In addition.

NOTE Confidence: 0.810913899999999

00:40:09.920 --> 00:40:13.256 I'd like to thank all of our colleagues.

NOTE Confidence: 0.810913899999999

00:40:13.260 --> 00:40:16.179 I know if miss people in this,

NOTE Confidence: 0.810913899999999

00:40:16.180 --> 00:40:18.260 but but Joakim Mike Hurwitz,

NOTE Confidence: 0.810913899999999

00:40:18.260 --> 00:40:19.124 inheritance Bondy,

NOTE Confidence: 0.810913899999999

00:40:19.124 --> 00:40:22.148 who have really contributed greatly and work

NOTE Confidence: 0.810913899999999

00:40:22.148 --> 00:40:24.929 real hard in moving these trials forward.

NOTE Confidence: 0.810913899999999

00:40:24.930 --> 00:40:26.598 Our research associates, particularly

NOTE Confidence: 0.810913899999999

00:40:26.598 --> 00:40:28.683 Shelby Carleo and Ebony Williams,

NOTE Confidence: 0.810913899999999

00:40:28.690 --> 00:40:31.186 who helped to see the patients,

NOTE Confidence: 0.810913899999999

00:40:31.190 --> 00:40:32.438 manage the data.

NOTE Confidence: 0.810913899999999

00:40:32.438 --> 00:40:33.270 And really,

NOTE Confidence: 0.810913899999999

00:40:33.270 --> 00:40:35.766 they're invaluable to our operation map.

NOTE Confidence: 0.810913899999999

00:40:35.770 --> 00:40:38.278 Piscatelli leftists about two weeks ago,

NOTE Confidence: 0.810913899999999

00:40:38.280 --> 00:40:40.020 but Kristen Fleshman has really

NOTE Confidence: 0.810913899999999

00:40:40.020 --> 00:40:42.530 done a great job and in helping

NOTE Confidence: 0.810913899999999

00:40:42.530 --> 00:40:44.636 us out during this time period.

NOTE Confidence: 0.810913899999999

00:40:44.640 --> 00:40:46.852 I know I've missed a bunch of

NOTE Confidence: 0.810913899999999

00:40:46.852 --> 00:40:49.224 different people in this area that have

NOTE Confidence: 0.810913899999999

00:40:49.224 --> 00:40:51.267 really helped us, and I apologize.

NOTE Confidence: 0.810913899999999

00:40:51.267 --> 00:40:52.962 Apologize to those who have

NOTE Confidence: 0.810913899999999

00:40:52.962 --> 00:40:54.540 not included in this slide,

NOTE Confidence: 0.810913899999999

00:40:54.540 --> 00:40:55.200 so Roy,

NOTE Confidence: 0.810913899999999

00:40:55.200 --> 00:40:56.520 thank you for your

NOTE Confidence: 0.8008387

00:40:56.520 --> 00:40:58.830 attention and turn it over to questions.

NOTE Confidence: 0.8008387

00:40:58.830 --> 00:41:00.951 OK thanks Dan. What a wonderful Tour

NOTE Confidence: 0.8008387

00:41:00.951 --> 00:41:03.447 de force in Geo Oncology I'll start.

NOTE Confidence: 0.8008387

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

NOTE Confidence: 0.8008387

00:41:08.320 --> 00:41:09.760 cancer chemistry colloquium.

NOTE Confidence: 0.8008387

00:41:09.760 --> 00:41:12.048 And we used to have that on Tuesday

NOTE Confidence: 0.8008387

00:41:12.048 --> 00:41:13.946 afternoons up on the hill. Scott Miller,

NOTE Confidence: 0.8008387

00:41:13.946 --> 00:41:15.892 the chair of Chemistry at the time,

NOTE Confidence: 0.8008387

00:41:15.900 --> 00:41:17.568 and, you know, we organize that.

NOTE Confidence: 0.8008387

00:41:17.570 --> 00:41:19.250 That's when Julie Boyer was here,

NOTE Confidence: 0.8008387

00:41:19.250 --> 00:41:21.514 and I'm glad to hear that the pro

NOTE Confidence: 0.8008387

00:41:21.514 --> 00:41:23.429 tech where it came out of that.

NOTE Confidence: 0.8008387

00:41:23.430 --> 00:41:25.510 So my question for you is how can

NOTE Confidence: 0.8008387

00:41:25.510 --> 00:41:27.899 we do more of these here at Yale?

NOTE Confidence: 0.8008387

00:41:27.900 --> 00:41:29.568 Then you have a great mechanism

NOTE Confidence: 0.8008387

00:41:29.568 --> 00:41:30.402 for clinical trials.

NOTE Confidence: 0.8008387

00:41:30.410 --> 00:41:32.078 You know that you've set up.

NOTE Confidence: 0.8008387

00:41:32.080 --> 00:41:33.748 You have a good patient population.

NOTE Confidence: 0.8008387

00:41:33.750 --> 00:41:35.591 What are the next step next agents

NOTE Confidence: 0.8008387

00:41:35.591 --> 00:41:36.820 coming through Yale Science?

NOTE Confidence: 0.8008387

00:41:36.820 --> 00:41:37.380 Do you

NOTE Confidence: 0.8245518

00:41:37.380 --> 00:41:39.804 think? Well, I mean, I think that there's.

NOTE Confidence: 0.8245518

00:41:39.810 --> 00:41:42.510 There's a next generation pro tech.

NOTE Confidence: 0.8245518

00:41:42.510 --> 00:41:45.486 That looks more active potentially than a RV.

NOTE Confidence: 0.8245518

00:41:45.490 --> 00:41:48.150 Then the every 110 and we're moving

NOTE Confidence: 0.8245518

00:41:48.150 --> 00:41:51.088 forth with that in the phase one trial,

NOTE Confidence: 0.8245518

00:41:51.090 --> 00:41:53.680 but I think that the real next

NOTE Confidence: 0.8245518

00:41:53.680 --> 00:41:56.309 generation will be had had a sequence.

NOTE Confidence: 0.8245518

00:41:56.310 --> 00:41:58.290 These had to combine these using

NOTE Confidence: 0.8245518

00:41:58.290 --> 00:42:00.526 our tumor bank to understand how

NOTE Confidence: 0.8245518

00:42:00.526 --> 00:42:02.646 to use these particular drugs.

NOTE Confidence: 0.8245518

00:42:02.650 --> 00:42:04.798 I think also.

NOTE Confidence: 0.8245518

00:42:04.800 --> 00:42:07.705 I didn't really get into this during

NOTE Confidence: 0.8245518

00:42:07.705 --> 00:42:11.030 the talk, but but how can we use?

NOTE Confidence: 0.8245518

00:42:11.030 --> 00:42:13.520 How can we include other ethnic

NOTE Confidence: 0.8245518

00:42:13.520 --> 00:42:15.180 groups in our treatments?

NOTE Confidence: 0.8245518

00:42:15.180 --> 00:42:17.250 It's actually an interesting phenomenon.

NOTE Confidence: 0.8245518

00:42:17.250 --> 00:42:19.215 Vet there have been publications

NOTE Confidence: 0.8245518

00:42:19.215 --> 00:42:21.180 looking at response rates in

NOTE Confidence: 0.8245518

00:42:21.252 --> 00:42:23.060 or survival to chemotherapy,

NOTE Confidence: 0.8245518

00:42:23.060 --> 00:42:25.135 immune therapy and next generation

NOTE Confidence: 0.8245518

00:42:25.135 --> 00:42:27.210 hormone therapy in African Americans.

NOTE Confidence: 0.8245518

00:42:27.210 --> 00:42:29.898 And it's actually better.

NOTE Confidence: 0.8245518

00:42:29.900 --> 00:42:32.612 And so we need to get the word

NOTE Confidence: 0.8245518

00:42:32.612 --> 00:42:35.289 out that these trials are open,

NOTE Confidence: 0.8245518

00:42:35.290 --> 00:42:37.275 that all should be included

NOTE Confidence: 0.8245518

00:42:37.275 --> 00:42:39.909 an that we don't want to see.

NOTE Confidence: 0.8245518

00:42:39.910 --> 00:42:42.190 People missed their opportunities to get

NOTE Confidence: 0.8245518

00:42:42.190 --> 00:42:44.918 drugs that they can move forward with,

NOTE Confidence: 0.8245518

00:42:44.920 --> 00:42:47.307 but I I was really surprised to

NOTE Confidence: 0.8245518

00:42:47.307 --> 00:42:49.828 see that this data we've actually

NOTE Confidence: 0.8245518

00:42:49.828 --> 00:42:52.654 been involved with this since our

NOTE Confidence: 0.8245518

00:42:52.654 --> 00:42:54.833 original swax these 2004 when we

NOTE Confidence: 0.8245518

00:42:54.833 --> 00:42:56.892 saw a very very big difference

NOTE Confidence: 0.8245518

00:42:56.892 --> 00:42:59.424 in in favor of African Americans

NOTE Confidence: 0.8245518

00:42:59.424 --> 00:43:00.690 with docetaxel chemotherapy.

NOTE Confidence: 0.8245518

00:43:00.690 --> 00:43:02.868 Numbers were too low to to

NOTE Confidence: 0.8245518

00:43:02.868 --> 00:43:04.320 make any real conclusions,

NOTE Confidence: 0.8245518

00:43:04.320 --> 00:43:06.558 but Susan Hobby is actually published

NOTE Confidence: 0.8245518

00:43:06.558 --> 00:43:08.777 on this with combined databases and

NOTE Confidence: 0.8245518

00:43:08.777 --> 00:43:11.080 this is something we really have to

NOTE Confidence: 0.8245518

00:43:11.080 --> 00:43:14.085 be to move forward with in terms of

NOTE Confidence: 0.8245518

00:43:14.085 --> 00:43:15.570 understanding how patients respond.

NOTE Confidence: 0.8258163

00:43:16.230 --> 00:43:17.560 Right, I can tell you,

NOTE Confidence: 0.8258163

00:43:17.560 --> 00:43:19.688 in my interim role here in the CTO,

NOTE Confidence: 0.8258163

00:43:19.690 --> 00:43:21.307 it's been quite noticeable to me that

NOTE Confidence: 0.8258163

00:43:21.307 --> 00:43:23.127 we do need to have more diversity

NOTE Confidence: 0.8258163

00:43:23.127 --> 00:43:24.741 in our populations and that means

NOTE Confidence: 0.8258163

00:43:24.798 --> 00:43:26.338 reaching out and building trust.

NOTE Confidence: 0.8258163

00:43:26.340 --> 00:43:28.725 And I know you've been doing some of that.

NOTE Confidence: 0.8258163

00:43:28.730 --> 00:43:30.128 You know, with the cultural ambassadors

NOTE Confidence: 0.8258163

00:43:30.128 --> 00:43:31.919 and other groups and providing navigators,

NOTE Confidence: 0.8258163

00:43:31.920 --> 00:43:33.789 we have a question from Darrell Martin.

NOTE Confidence: 0.8258163

00:43:33.790 --> 00:43:35.449 Renee, do you want to unmute Darrell

NOTE Confidence: 0.8258163

00:43:35.449 --> 00:43:37.510 so he can ask the question himself?

NOTE Confidence: 0.69033444

00:43:40.250 --> 00:43:40.760 Darrell.

NOTE Confidence: 0.9307016

00:43:44.660 --> 00:43:45.860 If not, I'll ask it.

NOTE Confidence: 0.8553526

00:43:50.740 --> 00:43:51.940 Well, actually I can ask you

NOTE Confidence: 0.8553526

00:43:51.940 --> 00:43:53.180 'cause you just raised your hand.

NOTE Confidence: 0.8123636

00:43:59.800 --> 00:44:02.923 OK, any other questions for for Dan Dan tell

NOTE Confidence: 0.8123636

00:44:02.923 --> 00:44:06.089 me a little bit about about your Darden.

NOTE Confidence: 0.8123636

00:44:06.090 --> 00:44:08.802 Now with Isaac Kim coming as the new

NOTE Confidence: 0.8123636

00:44:08.802 --> 00:44:11.640 chair of Urology, any plans to forge

NOTE Confidence: 0.8123636

00:44:11.640 --> 00:44:13.490 some new collaborations you know?

NOTE Confidence: 0.8123636

00:44:13.490 --> 00:44:15.710 Build out the multi modality presence?

NOTE Confidence: 0.8123636

00:44:15.710 --> 00:44:18.670 I know it's still early and he's just

NOTE Confidence: 0.8123636

00:44:18.670 --> 00:44:20.520 been announced, but some thoughts?

NOTE Confidence: 0.8123636

00:44:20.520 --> 00:44:21.260 Well, I

NOTE Confidence: 0.8123636

00:44:21.260 --> 00:44:23.850 I've had a couple of conversations already.

NOTE Confidence: 0.8123636

00:44:23.850 --> 00:44:26.524 You know he's he's really been one

NOTE Confidence: 0.8123636

00:44:26.524 --> 00:44:28.858 of the Champions. In looking at.

NOTE Confidence: 0.81962115

00:44:30.890 --> 00:44:33.900 Local treatment in terms of patients who

NOTE Confidence: 0.81962115

00:44:33.900 --> 00:44:36.480 have metastatic disease, so this actually

NOTE Confidence: 0.81962115

00:44:36.480 --> 00:44:39.490 has been known for quite some time.

NOTE Confidence: 0.81962115

00:44:39.490 --> 00:44:42.787 In fact, one of the sister presentations

NOTE Confidence: 0.81962115

00:44:42.787 --> 00:44:45.694 that original meeting at presentation of

NOTE Confidence: 0.81962115

00:44:45.694 --> 00:44:48.991 the texture data at ASCO demonstrated those

NOTE Confidence: 0.81962115

00:44:49.072 --> 00:44:52.186 patients who had a radical prostatectomy.

NOTE Confidence: 0.81962115

00:44:52.190 --> 00:44:55.030 As part of their history did better with

NOTE Confidence: 0.81962115

00:44:55.030 --> 00:44:56.907 chemotherapy than those who did not,

NOTE Confidence: 0.81962115

00:44:56.910 --> 00:44:59.269 and this may be a selection factor,

NOTE Confidence: 0.81962115

00:44:59.270 --> 00:45:00.950 but this has been observed

NOTE Confidence: 0.81962115

00:45:00.950 --> 00:45:01.958 by numerous investigators,

NOTE Confidence: 0.81962115

00:45:01.960 --> 00:45:04.095 so I zic is actually looking at

NOTE Confidence: 0.81962115

00:45:04.095 --> 00:45:05.670 a protocol he's bringing.

NOTE Confidence: 0.81962115

00:45:05.670 --> 00:45:08.505 It was with this with him to evaluate local

NOTE Confidence: 0.81962115

00:45:08.505 --> 00:45:10.730 treatment in terms of metastatic disease.

NOTE Confidence: 0.81962115

00:45:10.730 --> 00:45:12.070 Through these patients receive

NOTE Confidence: 0.81962115

00:45:12.070 --> 00:45:13.075 a radical prostatectomy.

NOTE Confidence: 0.81962115

00:45:13.080 --> 00:45:15.488 Often my patients will ask me that question

NOTE Confidence: 0.81962115

00:45:15.488 --> 00:45:17.797 should they get local radiation treatment.

NOTE Confidence: 0.81962115

00:45:17.800 --> 00:45:20.474 It's actually part of some of our

NOTE Confidence: 0.81962115

00:45:20.474 --> 00:45:22.559 treatment regimen's already to begin with.

NOTE Confidence: 0.81962115

00:45:22.560 --> 00:45:24.100 So he's going to bring a unique

NOTE Confidence: 0.81962115

00:45:24.100 --> 00:45:25.610 look at this particular area,

NOTE Confidence: 0.81962115

00:45:25.610 --> 00:45:27.038 and we're going to be collaborating

NOTE Confidence: 0.81962115

00:45:27.038 --> 00:45:28.697 on those trials as brothers as well

NOTE Confidence: 0.81962115

00:45:28.697 --> 00:45:30.237 as some other trials that will be

NOTE Confidence: 0.81962115

00:45:30.288 --> 00:45:31.700 targeting the androgen receptor.

NOTE Confidence: 0.7644819

00:45:33.450 --> 00:45:34.581 Excellent excellent yeah.

NOTE Confidence: 0.7644819

00:45:34.581 --> 00:45:37.605 He's already called me as to move start

NOTE Confidence: 0.7644819

00:45:37.605 --> 00:45:40.422 moving it through the CTL so we started OK.

NOTE Confidence: 0.7644819

00:45:40.430 --> 00:45:42.518 Each young Kim had a question.

NOTE Confidence: 0.7644819

00:45:42.520 --> 00:45:44.970 Dan at the time of castration resistance,

NOTE Confidence: 0.7644819

00:45:44.970 --> 00:45:47.406 either primary or secondary, do we do?

NOTE Confidence: 0.7644819

00:45:47.410 --> 00:45:49.498 We routinely sequence AR androgen receptor?

NOTE Confidence: 0.8559534

00:45:51.660 --> 00:45:53.736 So I I've been running, you know,

NOTE Confidence: 0.8559534

00:45:53.736 --> 00:45:55.404 routinely running this as part of

NOTE Confidence: 0.8559534

00:45:55.404 --> 00:45:57.256 a platform because we're looking to

NOTE Confidence: 0.8559534

00:45:57.256 --> 00:45:59.110 select these patients for the trial

NOTE Confidence: 0.8559534

00:45:59.170 --> 00:46:01.078 as part of routine clinical practice.

NOTE Confidence: 0.8559534

00:46:01.080 --> 00:46:03.388 The answer is no.

NOTE Confidence: 0.8559534

00:46:03.390 --> 00:46:06.211 I do not look at and receptor

NOTE Confidence: 0.8559534

00:46:06.211 --> 00:46:08.948 mutations or AR V7 and the reason

NOTE Confidence: 0.8559534

00:46:08.948 --> 00:46:12.268 why I don't look at it is that the.

NOTE Confidence: 0.8559534

00:46:12.270 --> 00:46:14.839 We do the trial that extra micro,

NOTE Confidence: 0.8559534

00:46:14.840 --> 00:46:17.132 which was RPI on this particular

NOTE Confidence: 0.8559534

00:46:17.132 --> 00:46:19.408 study number of years ago of

NOTE Confidence: 0.8559534

00:46:19.408 --> 00:46:21.078 a drug called Glitter Own,

NOTE Confidence: 0.8559534

00:46:21.080 --> 00:46:24.374 which was supposed to be active in a RV.

NOTE Confidence: 0.8559534

00:46:24.380 --> 00:46:26.228 7 positive patients an the selection

NOTE Confidence: 0.8559534

00:46:26.228 --> 00:46:27.953 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

NOTE Confidence: 0.7994135

00:47:46.562 --> 00:47:48.764 what's the best way to balance

NOTE Confidence: 0.7994135

00:47:48.764 --> 00:47:51.002 things in terms of our portfolio,

NOTE Confidence: 0.7994135

00:47:51.010 --> 00:47:53.834 so we are the phase three type trials

NOTE Confidence: 0.7994135

00:47:53.834 --> 00:47:56.739 or open should be open at the clip.

NOTE Confidence: 0.7994135

00:47:56.740 --> 00:47:59.813 That care centers we did have the

NOTE Confidence: 0.7994135

00:47:59.813 --> 00:48:02.877 Taxotere Pembroke trial open and we do

NOTE Confidence: 0.7994135

00:48:02.877 --> 00:48:05.373 have a Pembroke enzalutamide study open

NOTE Confidence: 0.7994135

00:48:05.454 --> 00:48:08.230 as well at some of the care centers.

NOTE Confidence: 0.7994135

00:48:08.230 --> 00:48:11.230 So we've been trying to expand those trials

NOTE Confidence: 0.7994135

00:48:11.230 --> 00:48:14.286 that are are are would normally be seen.

NOTE Confidence: 0.7994135

00:48:14.290 --> 00:48:16.190 In practice, we doing more.

NOTE Confidence: 0.7994135

00:48:16.190 --> 00:48:18.836 The phase one is tripe type trials.

NOTE Confidence: 0.7994135

00:48:18.840 --> 00:48:20.735 Here we actually have been

NOTE Confidence: 0.7994135

00:48:20.735 --> 00:48:22.630 putting patients on at Greenwich.

NOTE Confidence: 0.7994135

00:48:22.630 --> 00:48:26.308 One of our tax dear patients.

NOTE Confidence: 0.7994135

00:48:26.310 --> 00:48:27.562 On the Merck study,

NOTE Confidence: 0.7994135

00:48:27.562 --> 00:48:29.440 is was on there as well,

NOTE Confidence: 0.7994135

00:48:29.440 --> 00:48:31.856 so so we are looking to expand these

NOTE Confidence: 0.7994135

00:48:31.856 --> 00:48:34.140 trials out to all the different care

NOTE Confidence: 0.78489655

00:48:34.140 --> 00:48:36.018 centers. Great, OK, well we'll give

NOTE Confidence: 0.78489655

00:48:36.018 --> 00:48:37.580 Doctor Bothwell one more chance.

NOTE Confidence: 0.81234676

00:48:41.320 --> 00:48:43.259 If not, I think well will end,

NOTE Confidence: 0.81234676

00:48:43.260 --> 00:48:45.700 but I just have one thought as we end then

NOTE Confidence: 0.81234676

00:48:45.760 --> 00:48:47.965 it has been nine years and apologized.

NOTE Confidence: 0.81234676

00:48:47.970 --> 00:48:49.769 But you know, I've been here 10

NOTE Confidence: 0.81234676

00:48:49.769 --> 00:48:51.951 years and one of the first calls I

NOTE Confidence: 0.81234676

00:48:51.951 --> 00:48:53.941 got yellows from Jose Milo and who's

NOTE Confidence: 0.81234676

00:48:53.941 --> 00:48:55.985 house are are hospital bears his name

NOTE Confidence: 0.81234676

00:48:55.985 --> 00:48:58.232 and he says Roy why do all my friends

NOTE Confidence: 0.81234676

00:48:58.232 --> 00:49:00.580 have to go to New York to go in

NOTE Confidence: 0.81234676

00:49:00.580 --> 00:49:02.369 clinical trials for prostate cancer?

NOTE Confidence: 0.81234676

00:49:02.370 --> 00:49:04.309 And I said they will fix that.

NOTE Confidence: 0.81234676

00:49:04.310 --> 00:49:05.920 And Dan you certainly have and you

NOTE Confidence: 0.81234676

00:49:05.920 --> 00:49:07.908 made us the destination for prostate,

NOTE Confidence: 0.81234676

00:49:07.910 --> 00:49:09.198 bladder and other tumors.

NOTE Confidence: 0.81234676

00:49:09.198 --> 00:49:10.486 And congratulations on your

NOTE Confidence: 0.81234676

00:49:10.486 --> 00:49:12.169 program and I think many on the.

NOTE Confidence: 0.81234676

00:49:12.170 --> 00:49:14.858 The call here today will now perhaps have

NOTE Confidence: 0.81234676

00:49:14.858 --> 00:49:16.632 opportunities to collaborate with you

NOTE Confidence: 0.81234676

00:49:16.632 --> 00:49:19.061 'cause and build lab to clinic studies.

NOTE Confidence: 0.81234676

00:49:19.070 --> 00:49:21.140 So thank you all for coming

NOTE Confidence: 0.81234676

00:49:21.140 --> 00:49:22.520 to grand Rounds today.

NOTE Confidence: 0.81234676

00:49:22.520 --> 00:49:24.150 I'll just remind everyone that

NOTE Confidence: 0.81234676

00:49:24.150 --> 00:49:26.572 on June 25th in the morning we

NOTE Confidence: 0.81234676

00:49:26.572 --> 00:49:28.387 have our annual ASCO review.

NOTE Confidence: 0.81234676

00:49:28.390 --> 00:49:30.460 It is virtual again this year.

NOTE Confidence: 0.81234676

00:49:30.460 --> 00:49:31.792 It's a little shorter,

NOTE Confidence: 0.81234676

00:49:31.792 --> 00:49:34.599 but we're going to be reviewing many topics.

NOTE Confidence: 0.81234676

00:49:34.600 --> 00:49:37.008 Dan will be there hopefully as well,

NOTE Confidence: 0.81234676

00:49:37.010 --> 00:49:39.425 and actually for a very special treat,

NOTE Confidence: 0.81234676

00:49:39.430 --> 00:49:41.566 we're going to have Vince Devita

NOTE Confidence: 0.81234676

00:49:41.566 --> 00:49:42.990 interviewed by his daughter.

NOTE Confidence: 0.81234676

00:49:42.990 --> 00:49:44.290 Talking about the 50th anniversary

NOTE Confidence: 0.81234676

00:49:44.290 --> 00:49:45.590 of the National Cancer Act,

NOTE Confidence: 0.81234676

00:49:45.590 --> 00:49:47.410 so that's going to be very special,

NOTE Confidence: 0.81234676

00:49:47.410 --> 00:49:49.034 so I hope to see everyone there

NOTE Confidence: 0.81234676

00:49:49.034 --> 00:49:50.789 and have a good day everyone.