

WEBVTT

NOTE duration:"00:58:01.410000"

NOTE recognizability:0.928

NOTE language:en-us

NOTE Confidence: 0.948487290909091

00:00:00.000 --> 00:00:00.735 Good afternoon, everybody.

NOTE Confidence: 0.948487290909091

00:00:00.735 --> 00:00:02.840 I think we'll go ahead and get started.

NOTE Confidence: 0.948487290909091

00:00:02.840 --> 00:00:04.975 So greetings to everybody in

NOTE Confidence: 0.948487290909091

00:00:04.975 --> 00:00:07.760 the room and to everyone online.

NOTE Confidence: 0.948487290909091

00:00:07.760 --> 00:00:09.758 And welcome to Yale Cancer Center,

NOTE Confidence: 0.948487290909091

00:00:09.760 --> 00:00:11.755 Grand Rounds. My name is Pam Koons.

NOTE Confidence: 0.948487290909091

00:00:11.760 --> 00:00:13.025 I'm the director of the

NOTE Confidence: 0.948487290909091

00:00:13.025 --> 00:00:14.037 Center for GI Cancers,

NOTE Confidence: 0.948487290909091

00:00:14.040 --> 00:00:16.200 for those of you who do not know me.

NOTE Confidence: 0.948487290909091

00:00:16.200 --> 00:00:18.744 And it is a great honor to introduce

NOTE Confidence: 0.948487290909091

00:00:18.744 --> 00:00:21.599 my friend Doctor James Yao as the

NOTE Confidence: 0.948487290909091

00:00:21.599 --> 00:00:23.319 Norbert Schnog Endowed Lecturer.

NOTE Confidence: 0.948487290909091

00:00:23.320 --> 00:00:25.462 So Doctor Yao is a Professor and

NOTE Confidence: 0.948487290909091

00:00:25.462 --> 00:00:27.610 Chair in the Department of GI  
NOTE Confidence: 0.948487290909091

00:00:27.610 --> 00:00:29.545 Medical Oncology at the University  
NOTE Confidence: 0.948487290909091

00:00:29.545 --> 00:00:31.958 of MD Anderson Cancer Center,  
NOTE Confidence: 0.948487290909091

00:00:31.960 --> 00:00:34.306 and he received his medical degree  
NOTE Confidence: 0.948487290909091

00:00:34.306 --> 00:00:36.955 from Baylor College of Medicine and  
NOTE Confidence: 0.948487290909091

00:00:36.955 --> 00:00:39.653 completed his fellowship at MD Anderson.  
NOTE Confidence: 0.948487290909091

00:00:39.653 --> 00:00:42.308 So for the last two decades, Dr.  
NOTE Confidence: 0.948487290909091

00:00:42.308 --> 00:00:44.156 Yao and colleagues have really transformed  
NOTE Confidence: 0.948487290909091

00:00:44.156 --> 00:00:46.280 the field of neuroendocrine tumors.  
NOTE Confidence: 0.948487290909091

00:00:46.280 --> 00:00:50.332 So that is how I know him and he has led  
NOTE Confidence: 0.948487290909091

00:00:50.332 --> 00:00:52.997 practice changing randomized clinical trials,  
NOTE Confidence: 0.948487290909091

00:00:53.000 --> 00:00:55.724 specifically the family of radiant clinical  
NOTE Confidence: 0.948487290909091

00:00:55.724 --> 00:00:58.423 trials that include the drug everolimus  
NOTE Confidence: 0.948487290909091

00:00:58.423 --> 00:01:01.671 that led to FD approvals for pancreatic net,  
NOTE Confidence: 0.948487290909091

00:01:01.680 --> 00:01:04.648 lung net and GI and undercon tumors.  
NOTE Confidence: 0.948487290909091

00:01:04.650 --> 00:01:05.168 Doctor Yeah,

NOTE Confidence: 0.948487290909091

00:01:05.168 --> 00:01:06.722 I was also a strong advocate

NOTE Confidence: 0.948487290909091

00:01:06.722 --> 00:01:07.970 of mentoring and education.

NOTE Confidence: 0.948487290909091

00:01:07.970 --> 00:01:09.979 He is a founding member and past

NOTE Confidence: 0.948487290909091

00:01:09.979 --> 00:01:11.645 chairman of the North American

NOTE Confidence: 0.948487290909091

00:01:11.645 --> 00:01:13.500 Neuroendocrinic Tumor Society of which

NOTE Confidence: 0.948487290909091

00:01:13.500 --> 00:01:16.049 I am the president of this year.

NOTE Confidence: 0.948487290909091

00:01:16.050 --> 00:01:18.584 And then through that society can helped

NOTE Confidence: 0.948487290909091

00:01:18.584 --> 00:01:20.713 establish two young investigator awards

NOTE Confidence: 0.948487290909091

00:01:20.713 --> 00:01:23.168 that fund early career investigators.

NOTE Confidence: 0.948487290909091

00:01:23.170 --> 00:01:25.004 He's also the past chair of the

NOTE Confidence: 0.948487290909091

00:01:25.010 --> 00:01:27.260 NCIA and under consumer task force.

NOTE Confidence: 0.948487290909091

00:01:27.260 --> 00:01:28.728 And during his tenure,

NOTE Confidence: 0.948487290909091

00:01:28.728 --> 00:01:30.563 early career and female investigators

NOTE Confidence: 0.948487290909091

00:01:30.563 --> 00:01:33.012 led more than 50% of the multicentered

NOTE Confidence: 0.948487290909091

00:01:33.012 --> 00:01:34.708 clinical trials developed through

NOTE Confidence: 0.948487290909091

00:01:34.708 --> 00:01:36.420 that net task force.  
NOTE Confidence: 0.948487290909091

00:01:36.420 --> 00:01:39.579 I've known doctor Yes since I was a fellow.  
NOTE Confidence: 0.948487290909091

00:01:39.580 --> 00:01:41.701 I am one of those early career  
NOTE Confidence: 0.948487290909091

00:01:41.701 --> 00:01:43.312 investigators who benefited from his  
NOTE Confidence: 0.948487290909091

00:01:43.312 --> 00:01:44.932 mentorship and scholarship and had  
NOTE Confidence: 0.948487290909091

00:01:44.932 --> 00:01:47.085 the opportunity to lead one of the  
NOTE Confidence: 0.948487290909091

00:01:47.085 --> 00:01:49.147 randomized trials through the net task force.  
NOTE Confidence: 0.948487290909091

00:01:49.147 --> 00:01:51.716 So I'm grateful for you coming today  
NOTE Confidence: 0.948487290909091

00:01:51.716 --> 00:01:54.200 and joining us to speak on the 2nd  
NOTE Confidence: 0.948487290909091

00:01:54.200 --> 00:01:56.459 century of the land of small tumors.  
NOTE Confidence: 0.948487290909091

00:01:56.460 --> 00:01:56.979 So thank you,  
NOTE Confidence: 0.941371755555556

00:02:01.500 --> 00:02:04.588 Thank you so much for that kind introduction  
NOTE Confidence: 0.941371755555556

00:02:04.588 --> 00:02:07.260 and very glad to be here with you today.  
NOTE Confidence: 0.941371755555556

00:02:07.260 --> 00:02:09.836 So today I'm going to talk a little  
NOTE Confidence: 0.941371755555556

00:02:09.836 --> 00:02:12.139 bit about your endocrine tumors,  
NOTE Confidence: 0.941371755555556

00:02:12.140 --> 00:02:15.068 where we've been and some of the challenge

NOTE Confidence: 0.941371755555556

00:02:15.068 --> 00:02:17.839 remains and for you know what we need to.

NOTE Confidence: 0.941371755555556

00:02:17.840 --> 00:02:20.156 Make the next century even better

NOTE Confidence: 0.941371755555556

00:02:20.156 --> 00:02:24.053 than the what we've done so far and

NOTE Confidence: 0.941371755555556

00:02:24.053 --> 00:02:27.046 it's a plug for nanettes this this

NOTE Confidence: 0.941371755555556

00:02:27.046 --> 00:02:29.224 rainbow at this photograph was from

NOTE Confidence: 0.941371755555556

00:02:29.224 --> 00:02:31.492 one of the nanettes meetings which

NOTE Confidence: 0.941371755555556

00:02:31.492 --> 00:02:35.285 we held at the at the the Grand Tea

NOTE Confidence: 0.941371755555556

00:02:35.285 --> 00:02:39.160 Towns National Park and let's see

NOTE Confidence: 0.957026033333333

00:02:42.000 --> 00:02:44.409 here's my disclosures.

NOTE Confidence: 0.957026033333333

00:02:44.410 --> 00:02:46.906 So the field of neuroendocrine tumor

NOTE Confidence: 0.957026033333333

00:02:46.906 --> 00:02:49.509 started with open door for first

NOTE Confidence: 0.957026033333333

00:02:49.509 --> 00:02:52.687 described this entity about in 1907 he

NOTE Confidence: 0.957026033333333

00:02:52.687 --> 00:02:55.561 described this group disease is cancer

NOTE Confidence: 0.957026033333333

00:02:55.561 --> 00:02:59.603 like or part of what tumors are more slow

NOTE Confidence: 0.957026033333333

00:02:59.603 --> 00:03:02.609 growing than the typical carcinomas.

NOTE Confidence: 0.957026033333333

00:03:02.610 --> 00:03:06.292 The 1st century of net has been a a  
NOTE Confidence: 0.9570260333333333

00:03:06.292 --> 00:03:08.119 century where we've learned a lot about  
NOTE Confidence: 0.9570260333333333

00:03:08.119 --> 00:03:10.157 the Natural History of the disease.  
NOTE Confidence: 0.9570260333333333

00:03:10.160 --> 00:03:13.274 Understand a lot of the endocrine  
NOTE Confidence: 0.9570260333333333

00:03:13.274 --> 00:03:15.350 manifestations of neuroendocrine tumors  
NOTE Confidence: 0.9570260333333333

00:03:15.426 --> 00:03:18.965 and we also learn a lot about epidemiology  
NOTE Confidence: 0.9570260333333333

00:03:18.965 --> 00:03:22.040 of disease in semester biology.  
NOTE Confidence: 0.9570260333333333

00:03:22.040 --> 00:03:24.970 However, the number of therapeutic  
NOTE Confidence: 0.9570260333333333

00:03:24.970 --> 00:03:27.936 introduced over this period is  
NOTE Confidence: 0.9570260333333333

00:03:27.936 --> 00:03:32.451 actually relatively sparse prior to I  
NOTE Confidence: 0.9570260333333333

00:03:32.451 --> 00:03:34.677 would say the more recent approvals.  
NOTE Confidence: 0.9570260333333333

00:03:34.680 --> 00:03:37.404 There was only one drug that was FDA  
NOTE Confidence: 0.9570260333333333

00:03:37.404 --> 00:03:40.308 approved for oncologic control and that  
NOTE Confidence: 0.9570260333333333

00:03:40.308 --> 00:03:42.600 streptosis dosen for pancreatic net.  
NOTE Confidence: 0.9570260333333333

00:03:42.600 --> 00:03:46.124 There were two drugs approved for hormonal  
NOTE Confidence: 0.9570260333333333

00:03:46.124 --> 00:03:50.760 control of the neuroendocrine tumors.

NOTE Confidence: 0.957026033333333

00:03:50.760 --> 00:03:53.560 This is certainly not for lack of effort.

NOTE Confidence: 0.957026033333333

00:03:53.560 --> 00:03:56.815 This is a classic lecture by Chuck

NOTE Confidence: 0.957026033333333

00:03:56.815 --> 00:03:58.655 Mortell where he talks about his

NOTE Confidence: 0.957026033333333

00:03:58.655 --> 00:04:01.064 odyssey in the land of small tumors as

NOTE Confidence: 0.957026033333333

00:04:01.064 --> 00:04:03.440 you can see on the table on the right.

NOTE Confidence: 0.957026033333333

00:04:03.440 --> 00:04:06.095 There's been numerous agents that

NOTE Confidence: 0.957026033333333

00:04:06.095 --> 00:04:08.525 were studied but these chemotherapy

NOTE Confidence: 0.957026033333333

00:04:08.525 --> 00:04:11.255 agents did not really have that

NOTE Confidence: 0.957026033333333

00:04:11.255 --> 00:04:14.685 much activity with the exception of

NOTE Confidence: 0.957026033333333

00:04:14.685 --> 00:04:18.710 DTIC and streptozosin in pancreatic

NOTE Confidence: 0.957026033333333

00:04:18.710 --> 00:04:20.320 neuroendocrine tumors.

NOTE Confidence: 0.957026033333333

00:04:20.320 --> 00:04:22.438 Another thing you'll see is that

NOTE Confidence: 0.957026033333333

00:04:22.440 --> 00:04:24.462 that because you know this disease

NOTE Confidence: 0.957026033333333

00:04:24.462 --> 00:04:26.976 was thought to be rare and he that's

NOTE Confidence: 0.957026033333333

00:04:26.976 --> 00:04:29.628 why he used the the the term land

NOTE Confidence: 0.957026033333333

00:04:29.628 --> 00:04:30.789 of small tumors.  
NOTE Confidence: 0.9570260333333333

00:04:30.790 --> 00:04:34.590 The studies were actually very small and I  
NOTE Confidence: 0.9570260333333333

00:04:34.590 --> 00:04:37.670 think that really limited the the progress.  
NOTE Confidence: 0.9570260333333333

00:04:37.670 --> 00:04:39.728 These were all single arm studies  
NOTE Confidence: 0.9570260333333333

00:04:39.728 --> 00:04:41.997 and some of them only containing  
NOTE Confidence: 0.9570260333333333

00:04:41.997 --> 00:04:44.469 less than a handful of patients.  
NOTE Confidence: 0.930937682962963

00:04:47.550 --> 00:04:50.061 So one of the first things I think we  
NOTE Confidence: 0.930937682962963

00:04:50.061 --> 00:04:52.035 needed to understand about neuroendocrine  
NOTE Confidence: 0.930937682962963

00:04:52.035 --> 00:04:54.942 tumors is that the disease is probably  
NOTE Confidence: 0.930937682962963

00:04:54.942 --> 00:04:57.336 actually more common than we think.  
NOTE Confidence: 0.930937682962963

00:04:57.340 --> 00:05:00.439 One of the analysis we did in from  
NOTE Confidence: 0.930937682962963

00:05:00.439 --> 00:05:03.652 the SEAR database and we showed that  
NOTE Confidence: 0.930937682962963

00:05:03.652 --> 00:05:06.779 comparing to other malignant neoplasms  
NOTE Confidence: 0.930937682962963

00:05:06.780 --> 00:05:09.260 diagnose incidence of neuroendocrine  
NOTE Confidence: 0.930937682962963

00:05:09.260 --> 00:05:12.364 tumor is continually rising and since  
NOTE Confidence: 0.930937682962963

00:05:12.364 --> 00:05:15.220 this we have a kind of updated the data



NOTE Confidence: 0.930937682962963

00:05:15.220 --> 00:05:19.665 and in you know when when it was in 2004

NOTE Confidence: 0.930937682962963

00:05:19.665 --> 00:05:23.685 the incident was about 5 per 100,000,

NOTE Confidence: 0.930937682962963

00:05:23.685 --> 00:05:25.560 2012 about the.

NOTE Confidence: 0.930937682962963

00:05:25.560 --> 00:05:29.220 7 to per 100,000 and more more

NOTE Confidence: 0.930937682962963

00:05:29.220 --> 00:05:31.630 recent data would happen publish

NOTE Confidence: 0.930937682962963

00:05:31.714 --> 00:05:35.090 it is well above 8 per 100,000.

NOTE Confidence: 0.930937682962963

00:05:35.090 --> 00:05:37.045 Another thing that's different about

NOTE Confidence: 0.930937682962963

00:05:37.045 --> 00:05:39.373 this disease is because the disease

NOTE Confidence: 0.930937682962963

00:05:39.373 --> 00:05:41.239 is more slower growing patient live

NOTE Confidence: 0.930937682962963

00:05:41.239 --> 00:05:43.890 a lot a lot longer with the cancer.

NOTE Confidence: 0.930937682962963

00:05:43.890 --> 00:05:45.758 So essentially the prevalence

NOTE Confidence: 0.930937682962963

00:05:45.758 --> 00:05:48.560 statistic which is the number of

NOTE Confidence: 0.930937682962963

00:05:48.643 --> 00:05:50.506 patients who are potentially in

NOTE Confidence: 0.930937682962963

00:05:50.506 --> 00:05:52.802 need of care because there are life

NOTE Confidence: 0.930937682962963

00:05:52.802 --> 00:05:55.080 with disease is actually higher.

NOTE Confidence: 0.930937682962963

00:05:55.080 --> 00:05:58.020 So if you did limited duration  
NOTE Confidence: 0.930937682962963

00:05:58.020 --> 00:06:00.477 prevalence analysis which we did from  
NOTE Confidence: 0.930937682962963

00:06:00.477 --> 00:06:03.305 the SEAR data it the US prevalence  
NOTE Confidence: 0.930937682962963

00:06:03.305 --> 00:06:06.090 last we looked was above 170,000.  
NOTE Confidence: 0.930937682962963

00:06:06.090 --> 00:06:09.835 So certainly this is still at least  
NOTE Confidence: 0.930937682962963

00:06:09.835 --> 00:06:13.372 for the moment below the 200,000 cut  
NOTE Confidence: 0.930937682962963

00:06:13.372 --> 00:06:16.500 off which the FDA uses this definition  
NOTE Confidence: 0.930937682962963

00:06:16.500 --> 00:06:19.376 of rare disease and certainly if you  
NOTE Confidence: 0.930937682962963

00:06:19.376 --> 00:06:21.710 further divide you're in the consumer  
NOTE Confidence: 0.930937682962963

00:06:21.777 --> 00:06:23.985 into a subtypes that will remain.  
NOTE Confidence: 0.930937682962963

00:06:23.990 --> 00:06:27.110 Rare for quite a quite a long time.  
NOTE Confidence: 0.930937682962963

00:06:27.110 --> 00:06:29.909 So one of the question to think about is,  
NOTE Confidence: 0.930937682962963

00:06:29.910 --> 00:06:32.316 was this rising incidence and so  
NOTE Confidence: 0.930937682962963

00:06:32.316 --> 00:06:34.590 forth is what's going on here.  
NOTE Confidence: 0.930937682962963

00:06:34.590 --> 00:06:36.865 There are environmental factors that  
NOTE Confidence: 0.930937682962963

00:06:36.865 --> 00:06:39.140 are increasing the incidence of

NOTE Confidence: 0.930937682962963  
00:06:39.215 --> 00:06:41.867 neuroendocrine tumor or perhaps this is  
NOTE Confidence: 0.930937682962963  
00:06:41.867 --> 00:06:44.510 just better recognition of the disease.  
NOTE Confidence: 0.930937682962963  
00:06:44.510 --> 00:06:47.365 Certainly we are seeing more  
NOTE Confidence: 0.930937682962963  
00:06:47.365 --> 00:06:49.800 neuroendocrine tumors in some case  
NOTE Confidence: 0.930937682962963  
00:06:49.800 --> 00:06:52.810 related in the gastric urine the consumer.  
NOTE Confidence: 0.930937682962963  
00:06:52.810 --> 00:06:55.650 Related to use of PPI's,  
NOTE Confidence: 0.930937682962963  
00:06:55.650 --> 00:06:58.594 but I think for the most part these  
NOTE Confidence: 0.930937682962963  
00:06:58.594 --> 00:07:00.850 neuroendocrine tumor has always been there.  
NOTE Confidence: 0.930937682962963  
00:07:00.850 --> 00:07:03.167 So here are a couple of classic  
NOTE Confidence: 0.930937682962963  
00:07:03.167 --> 00:07:04.450 studies in two in,  
NOTE Confidence: 0.930937682962963  
00:07:04.450 --> 00:07:04.962 in,  
NOTE Confidence: 0.930937682962963  
00:07:04.962 --> 00:07:08.034 in Carcino tumors are really talking  
NOTE Confidence: 0.930937682962963  
00:07:08.034 --> 00:07:09.570 about intestinal neuroendocrine  
NOTE Confidence: 0.930937682962963  
00:07:09.647 --> 00:07:12.209 tumors are two studies that included  
NOTE Confidence: 0.930937682962963  
00:07:12.210 --> 00:07:14.850 15,000 autopsies and these tumors  
NOTE Confidence: 0.930937682962963

00:07:14.850 --> 00:07:18.380 are found in about 1% of autopsies.  
NOTE Confidence: 0.930937682962963

00:07:18.380 --> 00:07:21.050 So these are patient who died  
NOTE Confidence: 0.930937682962963

00:07:21.050 --> 00:07:22.560 from unrelated causes.  
NOTE Confidence: 0.930937682962963

00:07:22.560 --> 00:07:25.871 And most mostly lift out their natural  
NOTE Confidence: 0.930937682962963

00:07:25.871 --> 00:07:28.520 lifespan without having them diagnosed.  
NOTE Confidence: 0.930937682962963

00:07:28.520 --> 00:07:31.285 So really the question is not so  
NOTE Confidence: 0.930937682962963

00:07:31.285 --> 00:07:34.800 much whether they're increasing in  
NOTE Confidence: 0.930937682962963

00:07:34.800 --> 00:07:36.680 and what are environmental factors,  
NOTE Confidence: 0.930937682962963

00:07:36.680 --> 00:07:39.760 but what transforms some of these nine  
NOTE Confidence: 0.930937682962963

00:07:39.760 --> 00:07:42.656 small tumor into malignant ones but  
NOTE Confidence: 0.930937682962963

00:07:42.656 --> 00:07:44.160 pancreatic neurin different tumors.  
NOTE Confidence: 0.930937682962963

00:07:44.160 --> 00:07:46.600 There's one study that was in Hong Kong,  
NOTE Confidence: 0.930937682962963

00:07:46.600 --> 00:07:51.070 again 11,000 autopsy one in 1000.  
NOTE Confidence: 0.930937682962963

00:07:51.070 --> 00:07:53.428 Autopsy specimen had a pancreatic urine.  
NOTE Confidence: 0.930937682962963

00:07:53.430 --> 00:07:54.218 The consumer,  
NOTE Confidence: 0.930937682962963

00:07:54.218 --> 00:07:56.944 if you look for them compare this

NOTE Confidence: 0.930937682962963

00:07:56.944 --> 00:07:59.206 to a diagnosed instance more like

NOTE Confidence: 0.930937682962963

00:07:59.206 --> 00:08:02.255 in the range of maybe three to five

NOTE Confidence: 0.930937682962963

00:08:02.255 --> 00:08:03.747 per million per year.

NOTE Confidence: 0.930937682962963

00:08:03.750 --> 00:08:06.630 That tells you probably less than

NOTE Confidence: 0.930937682962963

00:08:06.630 --> 00:08:09.030 1% of pancrea and urine.

NOTE Confidence: 0.930937682962963

00:08:09.030 --> 00:08:11.995 The consumers that are present

NOTE Confidence: 0.930937682962963

00:08:11.995 --> 00:08:15.094 and in patients eventually become

NOTE Confidence: 0.930937682962963

00:08:15.094 --> 00:08:16.346 clinically relevant.

NOTE Confidence: 0.930937682962963

00:08:16.350 --> 00:08:18.252 This is posing a challenge for

NOTE Confidence: 0.930937682962963

00:08:18.252 --> 00:08:20.170 us as we move forward.

NOTE Confidence: 0.930937682962963

00:08:20.170 --> 00:08:23.000 Because the increased use of

NOTE Confidence: 0.930937682962963

00:08:23.000 --> 00:08:24.882 imaging nowadays you can hardly

NOTE Confidence: 0.930937682962963

00:08:24.882 --> 00:08:26.850 go to the ER with abdominal

NOTE Confidence: 0.938664642105263

00:08:26.920 --> 00:08:29.683 pain without leaving the ER with a CT scan.

NOTE Confidence: 0.938664642105263

00:08:29.690 --> 00:08:33.450 So we're finding a lot of small tiny

NOTE Confidence: 0.938664642105263

00:08:33.450 --> 00:08:34.635 pancreatic neuroendocrine tumors,  
NOTE Confidence: 0.938664642105263

00:08:34.635 --> 00:08:37.789 some of them in the head of pancreas  
NOTE Confidence: 0.938664642105263

00:08:37.789 --> 00:08:40.642 where if you try to operate on them may,  
NOTE Confidence: 0.938664642105263

00:08:40.650 --> 00:08:42.596 may, may be a quite a morbid  
NOTE Confidence: 0.938664642105263

00:08:42.596 --> 00:08:44.130 and higher risk procedure.  
NOTE Confidence: 0.938664642105263

00:08:44.130 --> 00:08:47.210 So understanding which of these can be  
NOTE Confidence: 0.938664642105263

00:08:47.210 --> 00:08:50.180 left alone and patients are going to.  
NOTE Confidence: 0.938664642105263

00:08:50.180 --> 00:08:51.560 Essentially lived with disease  
NOTE Confidence: 0.938664642105263

00:08:51.560 --> 00:08:52.940 in their natural lifespan,  
NOTE Confidence: 0.938664642105263

00:08:52.940 --> 00:08:55.306 which one is near to near that  
NOTE Confidence: 0.938664642105263

00:08:55.306 --> 00:08:57.668 really needs to intervene on is  
NOTE Confidence: 0.938664642105263

00:08:57.668 --> 00:09:00.212 going to be important going forward.  
NOTE Confidence: 0.938664642105263

00:09:00.220 --> 00:09:03.668 So the other thing that the with you know  
NOTE Confidence: 0.938664642105263

00:09:03.668 --> 00:09:05.748 this information about the incidence  
NOTE Confidence: 0.938664642105263

00:09:05.748 --> 00:09:08.180 and prevalence in your endocrine tumors  
NOTE Confidence: 0.938664642105263

00:09:08.180 --> 00:09:11.978 is that the patient advocacy groups,

NOTE Confidence: 0.938664642105263  
00:09:11.980 --> 00:09:14.404 you know in the past decades  
NOTE Confidence: 0.938664642105263  
00:09:14.404 --> 00:09:16.020 has really got engaged.  
NOTE Confidence: 0.938664642105263  
00:09:16.020 --> 00:09:17.830 There are the stories of  
NOTE Confidence: 0.938664642105263  
00:09:17.830 --> 00:09:19.278 patients who have had.  
NOTE Confidence: 0.938664642105263  
00:09:19.280 --> 00:09:21.660 Long history of symptom maybe  
NOTE Confidence: 0.938664642105263  
00:09:21.660 --> 00:09:24.040 that went undiagnosed for decades.  
NOTE Confidence: 0.938664642105263  
00:09:24.040 --> 00:09:27.163 So there's a there was a strive to see  
NOTE Confidence: 0.938664642105263  
00:09:27.163 --> 00:09:29.891 whether we can recognize the symptoms  
NOTE Confidence: 0.938664642105263  
00:09:29.891 --> 00:09:32.880 earlier and diagnose the cancer earlier.  
NOTE Confidence: 0.938664642105263  
00:09:32.880 --> 00:09:36.376 But the challenge is the symptoms that are  
NOTE Confidence: 0.938664642105263  
00:09:36.376 --> 00:09:39.080 associated with these tumors are fairly  
NOTE Confidence: 0.938664642105263  
00:09:39.080 --> 00:09:42.400 vague and common in the general population.  
NOTE Confidence: 0.938664642105263  
00:09:42.400 --> 00:09:44.698 So this is study we did  
NOTE Confidence: 0.938664642105263  
00:09:44.698 --> 00:09:46.230 from CR Medicare database.  
NOTE Confidence: 0.938664642105263  
00:09:46.230 --> 00:09:48.864 Essentially, looked at the year prior  
NOTE Confidence: 0.938664642105263

00:09:48.864 --> 00:09:51.430 to their neuron cancer diagnosis,  
NOTE Confidence: 0.938664642105263

00:09:51.430 --> 00:09:54.391 what kind of doctor do they go visit and  
NOTE Confidence: 0.938664642105263

00:09:54.391 --> 00:09:57.509 what sort of symptoms do they complain of?  
NOTE Confidence: 0.938664642105263

00:09:57.510 --> 00:09:59.382 You can see, well,  
NOTE Confidence: 0.938664642105263

00:09:59.382 --> 00:10:02.190 statistically significant for most of these.  
NOTE Confidence: 0.938664642105263

00:10:02.190 --> 00:10:03.810 There are differences in  
NOTE Confidence: 0.938664642105263

00:10:03.810 --> 00:10:05.025 rates of hypertension,  
NOTE Confidence: 0.938664642105263

00:10:05.030 --> 00:10:07.750 abdominal pain, heart failure,  
NOTE Confidence: 0.938664642105263

00:10:07.750 --> 00:10:09.159 diarrhea, and peripheral edema.  
NOTE Confidence: 0.938664642105263

00:10:09.159 --> 00:10:11.533 But if you try to look at a positive  
NOTE Confidence: 0.938664642105263

00:10:11.533 --> 00:10:13.083 predictive value of these symptoms  
NOTE Confidence: 0.938664642105263

00:10:13.083 --> 00:10:14.999 when you're in the current tumor.  
NOTE Confidence: 0.938664642105263

00:10:15.000 --> 00:10:16.065 They're all very,  
NOTE Confidence: 0.938664642105263

00:10:16.065 --> 00:10:17.840 very low because they're very  
NOTE Confidence: 0.938664642105263

00:10:17.840 --> 00:10:20.120 common in the general population.  
NOTE Confidence: 0.920688171333333

00:10:22.560 --> 00:10:24.942 The newer endocrine field also is



NOTE Confidence: 0.920688171333333  
00:10:24.942 --> 00:10:27.466 a field where the very terminology  
NOTE Confidence: 0.920688171333333  
00:10:27.466 --> 00:10:30.462 we or she used to describe the  
NOTE Confidence: 0.920688171333333  
00:10:30.462 --> 00:10:32.641 disease has been evolving in the  
NOTE Confidence: 0.920688171333333  
00:10:32.641 --> 00:10:35.256 in in the over the past decades.  
NOTE Confidence: 0.920688171333333  
00:10:35.256 --> 00:10:37.596 In the older time frame,  
NOTE Confidence: 0.920688171333333  
00:10:37.600 --> 00:10:40.040 the worst like carcinoy eyelid  
NOTE Confidence: 0.920688171333333  
00:10:40.040 --> 00:10:41.992 spells were commonly used.  
NOTE Confidence: 0.920688171333333  
00:10:42.000 --> 00:10:45.732 And it's moved to newer endocrine  
NOTE Confidence: 0.920688171333333  
00:10:45.732 --> 00:10:48.013 neoplasms and there's grading  
NOTE Confidence: 0.920688171333333  
00:10:48.013 --> 00:10:51.319 initially just grade 1-2 and now  
NOTE Confidence: 0.920688171333333  
00:10:51.319 --> 00:10:53.740 differentiation is added to add a  
NOTE Confidence: 0.920688171333333  
00:10:53.740 --> 00:10:56.150 historical context on why the the  
NOTE Confidence: 0.920688171333333  
00:10:56.150 --> 00:10:58.700 constant change almost feels like  
NOTE Confidence: 0.920688171333333  
00:10:58.700 --> 00:11:00.956 in terminology is that this field  
NOTE Confidence: 0.920688171333333  
00:11:00.956 --> 00:11:03.624 you know at the time when these  
NOTE Confidence: 0.920688171333333

00:11:03.624 --> 00:11:06.235 terminologies classification created was.  
NOTE Confidence: 0.920688171333333

00:11:06.235 --> 00:11:06.630 Relatively.  
NOTE Confidence: 0.920688171333333

00:11:06.630 --> 00:11:09.395 I think people didn't really know where  
NOTE Confidence: 0.920688171333333

00:11:09.395 --> 00:11:12.370 the right cutoff is in terms of the disease.  
NOTE Confidence: 0.920688171333333

00:11:12.370 --> 00:11:14.872 It's more based on consensus and  
NOTE Confidence: 0.920688171333333

00:11:14.872 --> 00:11:18.330 recurrence and relate the true biology.  
NOTE Confidence: 0.920688171333333

00:11:18.330 --> 00:11:20.830 What beginning to understand is  
NOTE Confidence: 0.920688171333333

00:11:20.830 --> 00:11:23.194 clearly there's two different group  
NOTE Confidence: 0.920688171333333

00:11:23.194 --> 00:11:24.908 of diseases well differentiated,  
NOTE Confidence: 0.920688171333333

00:11:24.908 --> 00:11:27.631 you're in the consumer grade 1-2 and  
NOTE Confidence: 0.920688171333333

00:11:27.631 --> 00:11:30.417 three and they're mostly grade 1-2 and  
NOTE Confidence: 0.920688171333333

00:11:30.417 --> 00:11:33.178 numerically and then the essentially  
NOTE Confidence: 0.920688171333333

00:11:33.178 --> 00:11:36.138 the poorly differentiated urine carcinomas.  
NOTE Confidence: 0.920688171333333

00:11:36.140 --> 00:11:38.390 Which is a completely different disease  
NOTE Confidence: 0.920688171333333

00:11:38.390 --> 00:11:41.099 that has nothing to do with the other,  
NOTE Confidence: 0.920688171333333

00:11:41.100 --> 00:11:41.555 right.

NOTE Confidence: 0.920688171333333  
00:11:41.555 --> 00:11:43.830 And there are also differences  
NOTE Confidence: 0.920688171333333  
00:11:43.830 --> 00:11:46.860 in terms of the primary site.  
NOTE Confidence: 0.920688171333333  
00:11:46.860 --> 00:11:49.132 We'll talk a little bit about the  
NOTE Confidence: 0.920688171333333  
00:11:49.132 --> 00:11:51.020 molecular landscape and genomics  
NOTE Confidence: 0.920688171333333  
00:11:51.020 --> 00:11:53.380 of the different primary sites,  
NOTE Confidence: 0.920688171333333  
00:11:53.380 --> 00:11:56.060 but they are characterized by  
NOTE Confidence: 0.920688171333333  
00:11:56.060 --> 00:11:58.740 relatively low tumor mutational burden,  
NOTE Confidence: 0.920688171333333  
00:11:58.740 --> 00:12:01.901 but these tumor actually has high  
NOTE Confidence: 0.920688171333333  
00:12:01.901 --> 00:12:05.106 high rates of chromosomal instability.  
NOTE Confidence: 0.920688171333333  
00:12:05.110 --> 00:12:07.990 You see instead of point mutations,  
NOTE Confidence: 0.920688171333333  
00:12:07.990 --> 00:12:11.110 a large scale chromosomal changes  
NOTE Confidence: 0.920688171333333  
00:12:11.110 --> 00:12:13.170 lung neuro endocrine tumor.  
NOTE Confidence: 0.920688171333333  
00:12:13.170 --> 00:12:16.571 The most common mutation see is M  
NOTE Confidence: 0.920688171333333  
00:12:16.571 --> 00:12:19.226 EM1 and the same with pancreas M EM1.  
NOTE Confidence: 0.920688171333333  
00:12:19.230 --> 00:12:23.120 But here you also see DAX and ATRX and  
NOTE Confidence: 0.920688171333333

00:12:23.120 --> 00:12:27.545 intestinal relatively few somatic mutations,  
NOTE Confidence: 0.920688171333333

00:12:27.550 --> 00:12:30.790 but you see frequent loss of chromosome 18,  
NOTE Confidence: 0.920688171333333

00:12:30.790 --> 00:12:32.149 the poorly differential  
NOTE Confidence: 0.920688171333333

00:12:32.149 --> 00:12:33.508 neuro endocrine tumor.  
NOTE Confidence: 0.920688171333333

00:12:33.510 --> 00:12:36.268 It's probably really a mixed bag a  
NOTE Confidence: 0.920688171333333

00:12:36.270 --> 00:12:39.318 lot of time these are essentially  
NOTE Confidence: 0.920688171333333

00:12:39.318 --> 00:12:42.390 transformed versions of adenocarcinoma,  
NOTE Confidence: 0.920688171333333

00:12:42.390 --> 00:12:44.470 occasionally transformed lower grade  
NOTE Confidence: 0.920688171333333

00:12:44.470 --> 00:12:47.590 tumor after certain types of therapy,  
NOTE Confidence: 0.920688171333333

00:12:47.590 --> 00:12:50.038 but they're characterized by a very  
NOTE Confidence: 0.920688171333333

00:12:50.038 --> 00:12:53.213 fast growth rate and mutation in TP53  
NOTE Confidence: 0.920688171333333

00:12:53.213 --> 00:12:57.854 and RV are the most common mutations.  
NOTE Confidence: 0.920688171333333

00:12:57.860 --> 00:13:00.068 So if you understand the genomics  
NOTE Confidence: 0.920688171333333

00:13:00.068 --> 00:13:01.172 of neuroendocrine tumors,  
NOTE Confidence: 0.920688171333333

00:13:01.180 --> 00:13:03.952 so one of the things we did is leverage  
NOTE Confidence: 0.920688171333333

00:13:03.952 --> 00:13:06.779 our large phase three clinical trials.

NOTE Confidence: 0.920688171333333

00:13:06.780 --> 00:13:09.668 We did a series of trials called radium

NOTE Confidence: 0.920688171333333

00:13:09.668 --> 00:13:11.738 trials looking at everolimus where

NOTE Confidence: 0.920688171333333

00:13:11.740 --> 00:13:14.988 over about 1000 patients across you

NOTE Confidence: 0.920688171333333

00:13:14.988 --> 00:13:17.064 know four studies were were enrolled

NOTE Confidence: 0.920688171333333

00:13:17.064 --> 00:13:19.178 and where we can get the tumor.

NOTE Confidence: 0.920688171333333

00:13:19.180 --> 00:13:24.510 We did a whole genome analysis.

NOTE Confidence: 0.920688171333333

00:13:24.510 --> 00:13:28.470 We saw relatively few somatic mutations,

NOTE Confidence: 0.920688171333333

00:13:28.470 --> 00:13:31.606 but what what is striking is the amount

NOTE Confidence: 0.920688171333333

00:13:31.606 --> 00:13:33.869 of largescale chromosomal changes

NOTE Confidence: 0.920688171333333

00:13:33.870 --> 00:13:36.720 that you see chromosomal gain and

NOTE Confidence: 0.920688171333333

00:13:36.720 --> 00:13:39.410 chromosomal loss and these actually

NOTE Confidence: 0.920688171333333

00:13:39.410 --> 00:13:42.310 have very significant prognostic value.

NOTE Confidence: 0.920688171333333

00:13:42.310 --> 00:13:45.010 So for example in pancreatic

NOTE Confidence: 0.920688171333333

00:13:45.010 --> 00:13:46.630 neuron different tumors,

NOTE Confidence: 0.920688171333333

00:13:46.630 --> 00:13:48.960 patient with high chromosomal instability

NOTE Confidence: 0.920688171333333

00:13:48.960 --> 00:13:51.834 actually have a much better prognosis

NOTE Confidence: 0.920688171333333

00:13:51.834 --> 00:13:54.199 in the advanced disease setting.

NOTE Confidence: 0.920688171333333

00:13:54.200 --> 00:13:56.279 And we'll talk about a little bit

NOTE Confidence: 0.920688171333333

00:13:56.280 --> 00:13:58.688 in the next few slides why that

NOTE Confidence: 0.920688171333333

00:13:58.688 --> 00:14:01.440 is because it is a specific you

NOTE Confidence: 0.920688171333333

00:14:01.440 --> 00:14:04.000 know carcinogenesis pathway that's

NOTE Confidence: 0.920688171333333

00:14:04.000 --> 00:14:06.320 this this is implying here.

NOTE Confidence: 0.920688171333333

00:14:06.320 --> 00:14:09.866 And then we see also those patients

NOTE Confidence: 0.920688171333333

00:14:09.866 --> 00:14:11.758 with intestinal neuroendocrine tumor

NOTE Confidence: 0.920688171333333

00:14:11.758 --> 00:14:15.052 with loss of chromosome 18 also have a

NOTE Confidence: 0.920688171333333

00:14:15.052 --> 00:14:17.880 far better prognosis than those who do

NOTE Confidence: 0.942621458823529

00:14:17.969 --> 00:14:20.559 not have a loss of chromosome 18

NOTE Confidence: 0.942621458823529

00:14:20.560 --> 00:14:23.446 whereas the loss of chromosome 3.

NOTE Confidence: 0.942621458823529

00:14:23.450 --> 00:14:26.708 On the lung neuron, different tumors

NOTE Confidence: 0.942621458823529

00:14:26.708 --> 00:14:29.970 pertains to a poor prognosis.

NOTE Confidence: 0.942621458823529

00:14:29.970 --> 00:14:32.914 So one of the things that really always

NOTE Confidence: 0.942621458823529

00:14:32.914 --> 00:14:35.324 short struck me is really what's going on

NOTE Confidence: 0.942621458823529

00:14:35.324 --> 00:14:37.169 with pancreatic neural in the consumer.

NOTE Confidence: 0.942621458823529

00:14:37.170 --> 00:14:38.958 It's really one of my favorite

NOTE Confidence: 0.942621458823529

00:14:38.958 --> 00:14:41.130 diseases in the sense there's so much,

NOTE Confidence: 0.942621458823529

00:14:41.130 --> 00:14:42.786 so much stuff here.

NOTE Confidence: 0.942621458823529

00:14:42.786 --> 00:14:45.951 So you see here when we sequence

NOTE Confidence: 0.942621458823529

00:14:45.951 --> 00:14:48.740 the pancreatic neural in the tumors.

NOTE Confidence: 0.942621458823529

00:14:48.740 --> 00:14:50.828 They roughly fall into three categories

NOTE Confidence: 0.942621458823529

00:14:50.828 --> 00:14:53.864 when you look at the host whole genome

NOTE Confidence: 0.942621458823529

00:14:53.864 --> 00:14:56.574 in terms of chromosomal changes.

NOTE Confidence: 0.942621458823529

00:14:56.580 --> 00:14:59.220 In the first group here, Group One,

NOTE Confidence: 0.942621458823529

00:14:59.220 --> 00:15:02.580 they lose one copy of 11 of

NOTE Confidence: 0.942621458823529

00:15:02.580 --> 00:15:04.899 the 22 chromosomes.

NOTE Confidence: 0.942621458823529

00:15:04.900 --> 00:15:06.784 In the second group,

NOTE Confidence: 0.942621458823529

00:15:06.784 --> 00:15:11.658 there's loss of 1 copy of the 11 chromosomes,

NOTE Confidence: 0.942621458823529

00:15:11.660 --> 00:15:14.330 11 one copy of 11 chromosomes.  
NOTE Confidence: 0.942621458823529

00:15:14.330 --> 00:15:18.086 And gain on the complementary 11  
NOTE Confidence: 0.942621458823529

00:15:18.090 --> 00:15:20.560 chromosomes and then there's a  
NOTE Confidence: 0.942621458823529

00:15:20.560 --> 00:15:23.706 group that are relatively stable in  
NOTE Confidence: 0.942621458823529

00:15:23.706 --> 00:15:26.090 terms of chromosomal abnormalities.  
NOTE Confidence: 0.942621458823529

00:15:26.090 --> 00:15:28.330 And on the bottom panel is little small.  
NOTE Confidence: 0.942621458823529

00:15:28.330 --> 00:15:30.402 So I'll just talk through it a  
NOTE Confidence: 0.942621458823529

00:15:30.402 --> 00:15:32.431 little bit and it's important in  
NOTE Confidence: 0.942621458823529

00:15:32.431 --> 00:15:34.567 the sense that you can actually  
NOTE Confidence: 0.942621458823529

00:15:34.567 --> 00:15:36.862 link these chromosomal changes to  
NOTE Confidence: 0.942621458823529

00:15:36.862 --> 00:15:39.202 specific mutations that are present  
NOTE Confidence: 0.942621458823529

00:15:39.210 --> 00:15:42.040 in if you look at this.  
NOTE Confidence: 0.942621458823529

00:15:42.040 --> 00:15:44.176 The chromosomal instability tumors  
NOTE Confidence: 0.942621458823529

00:15:44.176 --> 00:15:48.114 so that that's these are in Gray and  
NOTE Confidence: 0.942621458823529

00:15:48.114 --> 00:15:50.945 in red are essentially are in rich  
NOTE Confidence: 0.942621458823529

00:15:50.945 --> 00:15:54.080 for patients with M EM1 mutations.



NOTE Confidence: 0.942621458823529

00:15:54.080 --> 00:15:57.531 So what's the link between M EM1

NOTE Confidence: 0.942621458823529

00:15:57.531 --> 00:16:01.512 mutation and and this and the M EM1

NOTE Confidence: 0.942621458823529

00:16:01.512 --> 00:16:04.500 mutations is also linked with DAX

NOTE Confidence: 0.942621458823529

00:16:04.606 --> 00:16:09.520 mutations whereas the ATRX mutations.

NOTE Confidence: 0.942621458823529

00:16:09.520 --> 00:16:12.180 Essentially also involved in a TRX and

NOTE Confidence: 0.942621458823529

00:16:12.180 --> 00:16:14.838 DAX are involved in alternative links.

NOTE Confidence: 0.942621458823529

00:16:14.840 --> 00:16:18.848 Near telomeres can be associated with

NOTE Confidence: 0.942621458823529

00:16:18.848 --> 00:16:23.438 chromosome instability in absence of M EM1.

NOTE Confidence: 0.942621458823529

00:16:23.440 --> 00:16:26.976 So the ATRX by itself the mutation

NOTE Confidence: 0.942621458823529

00:16:26.976 --> 00:16:29.716 seems to drive this phenomenon.

NOTE Confidence: 0.942621458823529

00:16:29.720 --> 00:16:32.402 So so So what we see here is then

NOTE Confidence: 0.942621458823529

00:16:32.402 --> 00:16:35.903 you see DAX and ATRX mutations

NOTE Confidence: 0.942621458823529

00:16:35.903 --> 00:16:37.775 associated chromosomal instability.

NOTE Confidence: 0.942621458823529

00:16:37.780 --> 00:16:38.677 And you have,

NOTE Confidence: 0.942621458823529

00:16:38.677 --> 00:16:41.763 you know loss of 1 copy of 11 chromosome

NOTE Confidence: 0.942621458823529

00:16:41.763 --> 00:16:44.522 and gain on the complementary 11  
NOTE Confidence: 0.942621458823529

00:16:44.522 --> 00:16:46.832 chromosomes and the strong association  
NOTE Confidence: 0.942621458823529

00:16:46.832 --> 00:16:49.459 between men one mutation and DAX  
NOTE Confidence: 0.942621458823529

00:16:49.459 --> 00:16:51.909 in the combination of men one DAX  
NOTE Confidence: 0.942621458823529

00:16:51.909 --> 00:16:54.298 mutation with chromosome instability.  
NOTE Confidence: 0.942621458823529

00:16:54.300 --> 00:16:55.500 So what's going on here?  
NOTE Confidence: 0.942621458823529

00:16:55.500 --> 00:16:58.510 Why are we losing one copy of  
NOTE Confidence: 0.942621458823529

00:16:58.510 --> 00:17:01.819 11 chromosome and gaining on the  
NOTE Confidence: 0.942621458823529

00:17:01.819 --> 00:17:05.130 complementary 11 chromosomes?  
NOTE Confidence: 0.942621458823529

00:17:05.130 --> 00:17:06.450 For whatever reason,  
NOTE Confidence: 0.942621458823529

00:17:06.450 --> 00:17:08.210 you're essentially what's actually  
NOTE Confidence: 0.942621458823529

00:17:08.210 --> 00:17:11.842 going on is you're losing one copy of  
NOTE Confidence: 0.942621458823529

00:17:11.842 --> 00:17:14.450 11 chromosomes and this in some patients,  
NOTE Confidence: 0.942621458823529

00:17:14.450 --> 00:17:16.730 probably due to haploinsufficiency,  
NOTE Confidence: 0.942621458823529

00:17:16.730 --> 00:17:20.168 is leading to whole genome duplication.  
NOTE Confidence: 0.942621458823529

00:17:20.170 --> 00:17:25.245 So essentially these are copy neutral LOH.

NOTE Confidence: 0.942621458823529  
00:17:25.250 --> 00:17:29.018 They are occurring essentially in the  
NOTE Confidence: 0.942621458823529  
00:17:29.018 --> 00:17:31.990 game because the whole genome duplication.  
NOTE Confidence: 0.942621458823529  
00:17:31.990 --> 00:17:34.458 Is occurring in the  
NOTE Confidence: 0.942621458823529  
00:17:34.458 --> 00:17:36.309 complementary 11 chromosomes.  
NOTE Confidence: 0.942621458823529  
00:17:36.310 --> 00:17:38.150 So what's the story here?  
NOTE Confidence: 0.942621458823529  
00:17:38.150 --> 00:17:42.008 While the most common mutation in your  
NOTE Confidence: 0.942621458823529  
00:17:42.008 --> 00:17:44.462 endocrine tumor is man one specifically  
NOTE Confidence: 0.942621458823529  
00:17:44.462 --> 00:17:46.590 linked to pancreatic neuroendocrine  
NOTE Confidence: 0.942621458823529  
00:17:46.590 --> 00:17:49.670 tumors occurring roughly about 40%  
NOTE Confidence: 0.942621458823529  
00:17:49.670 --> 00:17:53.426 of patients and also associated with  
NOTE Confidence: 0.942621458823529  
00:17:53.426 --> 00:17:55.304 lung neuroendocrine tumors.  
NOTE Confidence: 0.942621458823529  
00:17:55.310 --> 00:17:58.598 What do we know about man one biology?  
NOTE Confidence: 0.942621458823529  
00:17:58.600 --> 00:18:01.440 It is certainly is epigenetic  
NOTE Confidence: 0.942621458823529  
00:18:01.440 --> 00:18:03.712 regulators involved in modulating  
NOTE Confidence: 0.942621458823529  
00:18:03.720 --> 00:18:06.850 P27 and it's actually involved  
NOTE Confidence: 0.942621458823529

00:18:06.850 --> 00:18:09.354 in controlling endocrine mass.  
NOTE Confidence: 0.942621458823529

00:18:09.360 --> 00:18:12.616 So this is a study done at Stanford  
NOTE Confidence: 0.942621458823529

00:18:12.616 --> 00:18:15.184 where the group looked at men  
NOTE Confidence: 0.942621458823529

00:18:15.184 --> 00:18:19.000 and in in mice doing pregnancy  
NOTE Confidence: 0.929103402777778

00:18:19.000 --> 00:18:21.814 and you can see that men and  
NOTE Confidence: 0.929103402777778

00:18:21.814 --> 00:18:24.117 expression goes down during pregnancy  
NOTE Confidence: 0.929103402777778

00:18:24.117 --> 00:18:27.135 and goes back up post pregnancy.  
NOTE Confidence: 0.929103402777778

00:18:27.140 --> 00:18:31.522 Associated with that is turning on cell  
NOTE Confidence: 0.929103402777778

00:18:31.522 --> 00:18:35.459 cycle and increase in endocrine mass.  
NOTE Confidence: 0.929103402777778

00:18:35.460 --> 00:18:39.619 And so there is a, you know there's  
NOTE Confidence: 0.929103402777778

00:18:39.619 --> 00:18:43.224 important biology here in prevention of  
NOTE Confidence: 0.929103402777778

00:18:43.224 --> 00:18:46.260 gestational diabetes related to men in  
NOTE Confidence: 0.916977357272727

00:18:48.300 --> 00:18:51.674 men in turns out is also an  
NOTE Confidence: 0.916977357272727

00:18:51.674 --> 00:18:54.190 important regulator of telomeres.  
NOTE Confidence: 0.916977357272727

00:18:54.190 --> 00:18:58.856 In the Nurses in the Prostate, Lung,  
NOTE Confidence: 0.916977357272727

00:18:58.856 --> 00:19:00.908 Colorectal Ovarian Cancer Screening

NOTE Confidence: 0.916977357272727

00:19:00.908 --> 00:19:03.893 Trial and Nurses Health Study that

NOTE Confidence: 0.916977357272727

00:19:03.893 --> 00:19:05.950 involved about 3600 patients,

NOTE Confidence: 0.916977357272727

00:19:05.950 --> 00:19:09.481 the group this group evaluated 743

NOTE Confidence: 0.916977357272727

00:19:09.481 --> 00:19:13.198 snips and try to correlate that with

NOTE Confidence: 0.916977357272727

00:19:13.198 --> 00:19:16.030 essentially peripheral blood telomere lens.

NOTE Confidence: 0.916977357272727

00:19:16.030 --> 00:19:18.638 The only gene that fell out to be

NOTE Confidence: 0.916977357272727

00:19:18.638 --> 00:19:20.550 important was actually men and.

NOTE Confidence: 0.916977357272727

00:19:20.550 --> 00:19:23.952 It was the most important implicated

NOTE Confidence: 0.916977357272727

00:19:23.952 --> 00:19:26.710 in control of telomere lens

NOTE Confidence: 0.916977357272727

00:19:26.710 --> 00:19:31.390 for for in in the study.

NOTE Confidence: 0.916977357272727

00:19:31.390 --> 00:19:34.270 So the story of telomeres,

NOTE Confidence: 0.916977357272727

00:19:34.270 --> 00:19:36.694 you know as you know the telomeres are

NOTE Confidence: 0.916977357272727

00:19:36.694 --> 00:19:39.470 in the caps and end of our chromosomes

NOTE Confidence: 0.916977357272727

00:19:39.470 --> 00:19:43.070 and Menon is driving cell cycle in here.

NOTE Confidence: 0.916977357272727

00:19:43.070 --> 00:19:45.765 The telomere lens is going to get

NOTE Confidence: 0.916977357272727

00:19:45.765 --> 00:19:48.870 short as telomere lens gets short.  
NOTE Confidence: 0.916977357272727

00:19:48.870 --> 00:19:51.214 Essentially usually the cancer  
NOTE Confidence: 0.916977357272727

00:19:51.214 --> 00:19:53.990 cell dies where you need to turn  
NOTE Confidence: 0.916977357272727

00:19:53.990 --> 00:19:56.046 on some way of maintenance of  
NOTE Confidence: 0.916977357272727

00:19:56.046 --> 00:19:57.870 telomere or Linston telomeres.  
NOTE Confidence: 0.916977357272727

00:19:57.870 --> 00:20:01.518 For most cancers this is essentially  
NOTE Confidence: 0.916977357272727

00:20:01.518 --> 00:20:03.342 activation of telomeres,  
NOTE Confidence: 0.916977357272727

00:20:03.350 --> 00:20:06.822 but in a few cancers and in in  
NOTE Confidence: 0.916977357272727

00:20:06.822 --> 00:20:08.430 pancreatic neuroendocrine tumors,  
NOTE Confidence: 0.916977357272727

00:20:08.430 --> 00:20:13.010 the mechanism that's gets gets gets activated  
NOTE Confidence: 0.916977357272727

00:20:13.010 --> 00:20:17.060 as alternative linsing of telomeres.  
NOTE Confidence: 0.916977357272727

00:20:17.060 --> 00:20:18.220 How do we know this?  
NOTE Confidence: 0.916977357272727

00:20:18.220 --> 00:20:21.220 This is some slice courtesy of  
NOTE Confidence: 0.916977357272727

00:20:21.220 --> 00:20:24.420 Christopher Heefy where he showed  
NOTE Confidence: 0.916977357272727

00:20:24.420 --> 00:20:26.852 essentially in neuro endocrine tumor  
NOTE Confidence: 0.916977357272727

00:20:26.852 --> 00:20:30.933 that has well typed Dax ATRX you see

NOTE Confidence: 0.916977357272727

00:20:30.933 --> 00:20:35.120 fairly normal telomere lens and when

NOTE Confidence: 0.916977357272727

00:20:35.120 --> 00:20:39.165 there is Dax or a TRX alterations

NOTE Confidence: 0.916977357272727

00:20:39.165 --> 00:20:42.169 you see these bright pink spots

NOTE Confidence: 0.916977357272727

00:20:42.169 --> 00:20:45.169 which are telomere specific fish.

NOTE Confidence: 0.916977357272727

00:20:45.170 --> 00:20:49.600 Showing a classic pattern associated

NOTE Confidence: 0.916977357272727

00:20:49.600 --> 00:20:53.130 with alternative listening of telomeres,

NOTE Confidence: 0.933544666666667

00:20:55.450 --> 00:20:59.076 the story on essentially alternative

NOTE Confidence: 0.933544666666667

00:20:59.076 --> 00:21:02.294 listening telomeres and DAX ATRX mutations

NOTE Confidence: 0.933544666666667

00:21:02.294 --> 00:21:06.088 is actually complex in terms of prognosis.

NOTE Confidence: 0.933544666666667

00:21:06.090 --> 00:21:09.282 Earlier on I showed you a slide

NOTE Confidence: 0.933544666666667

00:21:09.282 --> 00:21:11.476 where essentially the the.

NOTE Confidence: 0.933544666666667

00:21:11.476 --> 00:21:16.508 Mutation of DAX ATRX and and turning

NOTE Confidence: 0.933544666666667

00:21:16.508 --> 00:21:19.202 out ELT was associated with good

NOTE Confidence: 0.933544666666667

00:21:19.202 --> 00:21:22.357 prognosis in patients with advanced

NOTE Confidence: 0.933544666666667

00:21:22.357 --> 00:21:24.526 pancreatic neuroendocrine tumor.

NOTE Confidence: 0.933544666666667

00:21:24.530 --> 00:21:26.642 The situation is actually  
NOTE Confidence: 0.933544666666667

00:21:26.642 --> 00:21:29.266 reversed in the earlier disease.  
NOTE Confidence: 0.933544666666667

00:21:29.266 --> 00:21:32.410 Essentially what's going on is that  
NOTE Confidence: 0.933544666666667

00:21:32.410 --> 00:21:37.564 advanced disease the the DAX ATRX mutation.  
NOTE Confidence: 0.933544666666667

00:21:37.564 --> 00:21:40.623 Is marking a group of pancrea urine  
NOTE Confidence: 0.933544666666667

00:21:40.623 --> 00:21:44.377 the consumer who goes down a very  
NOTE Confidence: 0.933544666666667

00:21:44.377 --> 00:21:45.994 specific carcinogenic pathway,  
NOTE Confidence: 0.933544666666667

00:21:46.000 --> 00:21:48.868 whereas in in the earlier disease  
NOTE Confidence: 0.933544666666667

00:21:48.868 --> 00:21:51.362 this actually the IT pretends  
NOTE Confidence: 0.933544666666667

00:21:51.362 --> 00:21:53.797 to be a worst prognosis.  
NOTE Confidence: 0.933544666666667

00:21:53.800 --> 00:21:55.528 So this is a great study  
NOTE Confidence: 0.933544666666667

00:21:55.528 --> 00:21:57.040 that was done in men,  
NOTE Confidence: 0.933544666666667

00:21:57.040 --> 00:21:58.132 one families.  
NOTE Confidence: 0.933544666666667

00:21:58.132 --> 00:22:00.940 So these are patients with  
NOTE Confidence: 0.933544666666667

00:22:00.940 --> 00:22:04.040 familial mutations in M EM1.  
NOTE Confidence: 0.933544666666667

00:22:04.040 --> 00:22:06.637 What they're able to show is that.



NOTE Confidence: 0.93354466666667  
00:22:06.640 --> 00:22:09.160 When the tumors are small,  
NOTE Confidence: 0.93354466666667  
00:22:09.160 --> 00:22:12.892 you usually don't see DAX ETRX  
NOTE Confidence: 0.93354466666667  
00:22:12.892 --> 00:22:16.270 mutations and the DAX ETRX mutations  
NOTE Confidence: 0.93354466666667  
00:22:16.270 --> 00:22:19.760 occurs in tumors that are larger  
NOTE Confidence: 0.93354466666667  
00:22:19.760 --> 00:22:21.783 in this case and I think they  
NOTE Confidence: 0.93354466666667  
00:22:21.783 --> 00:22:24.039 use a cutoff about 3 centimeters  
NOTE Confidence: 0.93354466666667  
00:22:24.040 --> 00:22:26.760 and also happens in patients  
NOTE Confidence: 0.93354466666667  
00:22:26.760 --> 00:22:29.480 who have lymph node metastasis.  
NOTE Confidence: 0.93354466666667  
00:22:29.480 --> 00:22:32.720 So likely what's going on is  
NOTE Confidence: 0.93354466666667  
00:22:32.720 --> 00:22:35.297 that as the these tumor.  
NOTE Confidence: 0.93354466666667  
00:22:35.297 --> 00:22:38.291 Are driven by men one to  
NOTE Confidence: 0.93354466666667  
00:22:38.291 --> 00:22:40.770 proliferate these benign tumors.  
NOTE Confidence: 0.93354466666667  
00:22:40.770 --> 00:22:43.890 The tilar mirrors are getting shorter  
NOTE Confidence: 0.93354466666667  
00:22:43.890 --> 00:22:46.896 and the ones who are able to turn on  
NOTE Confidence: 0.93354466666667  
00:22:46.896 --> 00:22:48.818 tilar mirror maintenance throughout  
NOTE Confidence: 0.93354466666667

00:22:48.818 --> 00:22:52.325 are the ones that gets larger and  
NOTE Confidence: 0.933544666666667

00:22:52.411 --> 00:22:54.970 then lead to regional metastasis.  
NOTE Confidence: 0.934383283333333

00:22:58.970 --> 00:23:02.300 So again, this is just showing  
NOTE Confidence: 0.934383283333333

00:23:02.300 --> 00:23:05.219 the same in terms of A.  
NOTE Confidence: 0.934383283333333

00:23:05.220 --> 00:23:07.660 In a recurrencefree survival graph,  
NOTE Confidence: 0.934383283333333

00:23:07.660 --> 00:23:09.856 those who are turning on health  
NOTE Confidence: 0.934383283333333

00:23:09.860 --> 00:23:12.460 in the localized setting where  
NOTE Confidence: 0.934383283333333

00:23:12.460 --> 00:23:14.986 they have three section have  
NOTE Confidence: 0.934383283333333

00:23:14.986 --> 00:23:17.216 a little bit poor prognosis.  
NOTE Confidence: 0.93773775

00:23:20.500 --> 00:23:22.428 Next I'm going to shift gear a little  
NOTE Confidence: 0.93773775

00:23:22.428 --> 00:23:25.075 bit and talk about essentially on the  
NOTE Confidence: 0.93773775

00:23:25.075 --> 00:23:28.316 clinical side the development of new  
NOTE Confidence: 0.93773775

00:23:28.316 --> 00:23:31.156 novel therapies for neuroendocrine tumors.  
NOTE Confidence: 0.93773775

00:23:31.160 --> 00:23:34.680 So essentially prior to 2007,  
NOTE Confidence: 0.93773775

00:23:34.680 --> 00:23:37.194 we only had Streptozosin for your  
NOTE Confidence: 0.93773775

00:23:37.194 --> 00:23:40.000 in the contumor of the pancreas.

NOTE Confidence: 0.93773775

00:23:40.000 --> 00:23:42.340 And since then you really have

NOTE Confidence: 0.93773775

00:23:42.340 --> 00:23:45.496 seen a lot of new agents showing

NOTE Confidence: 0.93773775

00:23:45.496 --> 00:23:48.460 activity getting FDA approved for

NOTE Confidence: 0.93773775

00:23:48.460 --> 00:23:50.960 having positive phase three trials.

NOTE Confidence: 0.93773775

00:23:50.960 --> 00:23:54.696 And I think a key thing here that

NOTE Confidence: 0.93773775

00:23:54.696 --> 00:23:57.517 happened really related to one of the

NOTE Confidence: 0.93773775

00:23:57.517 --> 00:23:59.470 meetings in Pam you were involved with.

NOTE Confidence: 0.93773775

00:23:59.470 --> 00:24:03.395 Was the first in a CTPM meeting sponsored

NOTE Confidence: 0.93773775

00:24:03.395 --> 00:24:06.116 by NCI and the importance of that

NOTE Confidence: 0.93773775

00:24:06.116 --> 00:24:09.070 meeting is really to come to consensus.

NOTE Confidence: 0.93773775

00:24:09.070 --> 00:24:11.966 What is the right kind of clinical trial

NOTE Confidence: 0.93773775

00:24:11.966 --> 00:24:14.427 design when you're in the consumers,

NOTE Confidence: 0.93773775

00:24:14.430 --> 00:24:16.710 what are the correct endpoints?

NOTE Confidence: 0.93773775

00:24:16.710 --> 00:24:18.622 There's a recognition progression,

NOTE Confidence: 0.93773775

00:24:18.622 --> 00:24:21.012 free survival is probably the

NOTE Confidence: 0.93773775

00:24:21.012 --> 00:24:23.108 right endpoint or in,  
NOTE Confidence: 0.93773775

00:24:23.108 --> 00:24:25.603 but the phase three trials  
NOTE Confidence: 0.93773775

00:24:25.603 --> 00:24:27.100 are are recommended.  
NOTE Confidence: 0.93773775

00:24:27.100 --> 00:24:29.284 Overall survival trials,  
NOTE Confidence: 0.93773775

00:24:29.284 --> 00:24:30.740 neuroendocrine tumors,  
NOTE Confidence: 0.93773775

00:24:30.740 --> 00:24:33.660 we came that out in doing the meeting  
NOTE Confidence: 0.93773775

00:24:33.660 --> 00:24:36.408 and realized they will require a  
NOTE Confidence: 0.93773775

00:24:36.408 --> 00:24:39.209 probably about two to 3000 patients  
NOTE Confidence: 0.93773775

00:24:39.209 --> 00:24:42.737 and probably 8 to 10 years to execute.  
NOTE Confidence: 0.93773775

00:24:42.740 --> 00:24:46.625 So that that's why you will see  
NOTE Confidence: 0.93773775

00:24:46.625 --> 00:24:49.796 in the subsequent slide most of  
NOTE Confidence: 0.93773775

00:24:49.796 --> 00:24:52.334 the approved agents are able to  
NOTE Confidence: 0.93773775

00:24:52.334 --> 00:24:54.086 then demonstrate PFS benefit.  
NOTE Confidence: 0.93773775

00:24:54.090 --> 00:24:55.638 But we don't have quite a  
NOTE Confidence: 0.93773775

00:24:55.638 --> 00:24:57.170 large sample size needed that  
NOTE Confidence: 0.93773775

00:24:57.170 --> 00:24:58.490 demonstrates survival benefit

NOTE Confidence: 0.945672246923077

00:25:02.050 --> 00:25:04.492 going going into the the systemic

NOTE Confidence: 0.945672246923077

00:25:04.492 --> 00:25:06.762 randomized space free trials are you

NOTE Confidence: 0.945672246923077

00:25:06.762 --> 00:25:09.066 know we you're going to talk to them

NOTE Confidence: 0.945672246923077

00:25:09.141 --> 00:25:11.565 a little bit about different targets.

NOTE Confidence: 0.945672246923077

00:25:11.570 --> 00:25:13.598 So the first targets we'll talk

NOTE Confidence: 0.945672246923077

00:25:13.598 --> 00:25:15.610 about is the Smestan receptor.

NOTE Confidence: 0.945672246923077

00:25:15.610 --> 00:25:18.884 For a long time prior to this Smestan

NOTE Confidence: 0.945672246923077

00:25:18.884 --> 00:25:21.580 receptor targeting was Octreotype.

NOTE Confidence: 0.945672246923077

00:25:21.580 --> 00:25:24.016 Was approved for control of Carson

NOTE Confidence: 0.945672246923077

00:25:24.016 --> 00:25:26.453 syndrome it relief flushing and diarrhea

NOTE Confidence: 0.945672246923077

00:25:26.453 --> 00:25:28.858 in probably about 70% of the patients.

NOTE Confidence: 0.945672246923077

00:25:28.858 --> 00:25:31.415 But there are a lot of back and

NOTE Confidence: 0.945672246923077

00:25:31.415 --> 00:25:33.461 forth debate as to whether actually

NOTE Confidence: 0.945672246923077

00:25:33.461 --> 00:25:36.450 or not is slow cancer grows and it

NOTE Confidence: 0.945672246923077

00:25:36.450 --> 00:25:38.580 was almost like a little religion

NOTE Confidence: 0.945672246923077

00:25:38.580 --> 00:25:40.915 people either believe it or we they  
NOTE Confidence: 0.945672246923077

00:25:40.915 --> 00:25:42.672 they didn't but what was important  
NOTE Confidence: 0.945672246923077

00:25:42.672 --> 00:25:44.892 is you just need to actually do the  
NOTE Confidence: 0.945672246923077

00:25:44.892 --> 00:25:47.712 trial it turns out and in this phase  
NOTE Confidence: 0.945672246923077

00:25:47.712 --> 00:25:50.788 three trial that's done by the.  
NOTE Confidence: 0.945672246923077

00:25:50.790 --> 00:25:55.718 A multicenter German trial in in patients  
NOTE Confidence: 0.945672246923077

00:25:55.718 --> 00:25:59.509 were relatively newly diagnosed with  
NOTE Confidence: 0.945672246923077

00:25:59.510 --> 00:26:01.530 small bowel neuroendocrine tumor.  
NOTE Confidence: 0.945672246923077

00:26:01.530 --> 00:26:04.055 They were able to demonstrate  
NOTE Confidence: 0.945672246923077

00:26:04.055 --> 00:26:06.388 improvement progression free survival.  
NOTE Confidence: 0.945672246923077

00:26:06.390 --> 00:26:08.922 A similar trial was land Realty  
NOTE Confidence: 0.945672246923077

00:26:08.922 --> 00:26:11.709 was conducted as a larger trial  
NOTE Confidence: 0.945672246923077

00:26:11.710 --> 00:26:14.152 and included a broader group of  
NOTE Confidence: 0.945672246923077

00:26:14.152 --> 00:26:15.780 patients including pancreatic and  
NOTE Confidence: 0.945672246923077

00:26:15.844 --> 00:26:17.659 rectal neuroendocrine tumors.  
NOTE Confidence: 0.945672246923077

00:26:17.660 --> 00:26:19.775 And again showing significant benefit

NOTE Confidence: 0.945672246923077

00:26:19.775 --> 00:26:22.540 in terms of progression free survival.

NOTE Confidence: 0.945672246923077

00:26:22.540 --> 00:26:24.840 Notice however the hazard ratio

NOTE Confidence: 0.945672246923077

00:26:24.840 --> 00:26:27.580 for the octerotized study was a

NOTE Confidence: 0.945672246923077

00:26:27.580 --> 00:26:29.752 little bit lower than the hazard

NOTE Confidence: 0.945672246923077

00:26:29.752 --> 00:26:32.499 ratio for the land real time study.

NOTE Confidence: 0.945672246923077

00:26:32.500 --> 00:26:36.516 This is probably a by byproduct in terms

NOTE Confidence: 0.945672246923077

00:26:36.516 --> 00:26:40.618 of the way the trial were executed.

NOTE Confidence: 0.945672246923077

00:26:40.620 --> 00:26:43.980 It turns out the octerotized study

NOTE Confidence: 0.945672246923077

00:26:43.980 --> 00:26:46.220 was permanent terminated early.

NOTE Confidence: 0.945672246923077

00:26:46.220 --> 00:26:50.240 At interim analysis and in there's

NOTE Confidence: 0.945672246923077

00:26:50.240 --> 00:26:52.646 been subsequent publications and

NOTE Confidence: 0.945672246923077

00:26:52.646 --> 00:26:55.311 analysing analysis of popular population

NOTE Confidence: 0.945672246923077

00:26:55.311 --> 00:26:57.796 of studies that can demonstrate

NOTE Confidence: 0.945672246923077

00:26:57.796 --> 00:27:00.628 while when you terminate a study

NOTE Confidence: 0.945672246923077

00:27:00.628 --> 00:27:03.178 early for outstanding efficacy,

NOTE Confidence: 0.945672246923077

00:27:03.180 --> 00:27:06.046 you tend to overestimate the the  
NOTE Confidence: 0.945672246923077

00:27:06.046 --> 00:27:08.376 magnitude of the treatment effect.  
NOTE Confidence: 0.945672246923077

00:27:08.380 --> 00:27:12.340 And that's just a you know a byproduct  
NOTE Confidence: 0.945672246923077

00:27:12.340 --> 00:27:14.090 of our early termination because  
NOTE Confidence: 0.945672246923077

00:27:14.090 --> 00:27:16.197 when you terminate a study early.  
NOTE Confidence: 0.945672246923077

00:27:16.200 --> 00:27:19.000 You preserve your ability to  
NOTE Confidence: 0.945672246923077

00:27:19.000 --> 00:27:20.680 test the hypothesis,  
NOTE Confidence: 0.945672246923077

00:27:20.680 --> 00:27:22.924 but not the ability to estimate  
NOTE Confidence: 0.945672246923077

00:27:22.924 --> 00:27:25.000 the magnitude of treatment benefit.  
NOTE Confidence: 0.847688196363636

00:27:27.120 --> 00:27:29.910 Another way to term to target  
NOTE Confidence: 0.847688196363636

00:27:29.910 --> 00:27:32.594 some mass and receptor is PRRT,  
NOTE Confidence: 0.847688196363636

00:27:32.594 --> 00:27:35.918 which really has become very well,  
NOTE Confidence: 0.847688196363636

00:27:35.920 --> 00:27:39.119 you know, widely used at this point.  
NOTE Confidence: 0.847688196363636

00:27:39.120 --> 00:27:40.824 Again, in the earlier  
NOTE Confidence: 0.847688196363636

00:27:40.824 --> 00:27:43.452 development of PRRT it was not.  
NOTE Confidence: 0.847688196363636

00:27:43.452 --> 00:27:47.500 It was a lot of a single single



NOTE Confidence: 0.847688196363636

00:27:47.500 --> 00:27:49.850 institution studies and you have

NOTE Confidence: 0.847688196363636

00:27:49.850 --> 00:27:52.336 these publications in high impact

NOTE Confidence: 0.847688196363636

00:27:52.336 --> 00:27:54.966 journals where they purportedly report

NOTE Confidence: 0.847688196363636

00:27:54.966 --> 00:27:59.070 a phase two study of 1000 patients.

NOTE Confidence: 0.847688196363636

00:27:59.070 --> 00:27:59.994 And you know,

NOTE Confidence: 0.847688196363636

00:27:59.994 --> 00:28:01.842 but actually what was needed for

NOTE Confidence: 0.847688196363636

00:28:01.842 --> 00:28:03.397 really demonstrating benefit and

NOTE Confidence: 0.847688196363636

00:28:03.397 --> 00:28:05.767 approval is a randomized phase three

NOTE Confidence: 0.847688196363636

00:28:05.767 --> 00:28:08.074 trial which you can do actually was

NOTE Confidence: 0.847688196363636

00:28:08.074 --> 00:28:10.940 far fewer than thousand patients.

NOTE Confidence: 0.847688196363636

00:28:10.940 --> 00:28:13.256 So this takes advantage of the

NOTE Confidence: 0.847688196363636

00:28:13.256 --> 00:28:15.239 fact that semastin receptors are

NOTE Confidence: 0.847688196363636

00:28:15.239 --> 00:28:17.079 present on your endocrine cancer

NOTE Confidence: 0.847688196363636

00:28:17.079 --> 00:28:19.952 cells in 7080% of the cases.

NOTE Confidence: 0.847688196363636

00:28:19.952 --> 00:28:22.084 Specifically for semastin receptor

NOTE Confidence: 0.847688196363636

00:28:22.084 --> 00:28:25.130 2 when the lichen binds to  
NOTE Confidence: 0.847688196363636

00:28:25.130 --> 00:28:27.138 the receptor is internalized.  
NOTE Confidence: 0.847688196363636

00:28:27.140 --> 00:28:27.806 So.  
NOTE Confidence: 0.847688196363636

00:28:27.806 --> 00:28:31.615 So these agents essentially takes a  
NOTE Confidence: 0.847688196363636

00:28:31.615 --> 00:28:34.940 Lutetian 177 and taking into the cell  
NOTE Confidence: 0.847688196363636

00:28:34.940 --> 00:28:37.298 and leading to very good efficacy.  
NOTE Confidence: 0.95132334

00:28:40.790 --> 00:28:43.838 There's also a role for targeted  
NOTE Confidence: 0.95132334

00:28:43.838 --> 00:28:45.870 therapy in neuroendocrine tumors.  
NOTE Confidence: 0.95132334

00:28:45.870 --> 00:28:48.814 One of the drugs that we were involved  
NOTE Confidence: 0.95132334

00:28:48.814 --> 00:28:51.007 in developing is everolimus of  
NOTE Confidence: 0.95132334

00:28:51.007 --> 00:28:53.542 affinitor targeting the emptor pathway.  
NOTE Confidence: 0.95132334

00:28:53.542 --> 00:28:57.167 The Radian 3 trial was the first  
NOTE Confidence: 0.95132334

00:28:57.167 --> 00:28:59.838 to report out and for pancreatic  
NOTE Confidence: 0.95132334

00:28:59.838 --> 00:29:02.742 neuroendocrine tumors and here you saw  
NOTE Confidence: 0.95132334

00:29:02.742 --> 00:29:05.421 a benefiting progression free survival  
NOTE Confidence: 0.95132334

00:29:05.421 --> 00:29:09.710 from median 4.6 months to 11 months.

NOTE Confidence: 0.95132334

00:29:09.710 --> 00:29:12.746 And hazard ratio was .35 here

NOTE Confidence: 0.95132334

00:29:12.750 --> 00:29:15.125 in overall survival because the

NOTE Confidence: 0.95132334

00:29:15.125 --> 00:29:17.912 crossover we did our PFST analysis

NOTE Confidence: 0.95132334

00:29:17.912 --> 00:29:19.676 rank preserving structure failure

NOTE Confidence: 0.95132334

00:29:19.676 --> 00:29:22.256 time showing like there's a likely

NOTE Confidence: 0.95132334

00:29:22.256 --> 00:29:23.748 benefit in overall survival,

NOTE Confidence: 0.95132334

00:29:23.750 --> 00:29:27.268 but in because of the the crossover

NOTE Confidence: 0.95132334

00:29:27.268 --> 00:29:29.656 these such studies and not these

NOTE Confidence: 0.95132334

00:29:29.656 --> 00:29:31.378 studies are really designed

NOTE Confidence: 0.95132334

00:29:31.378 --> 00:29:33.350 to evaluate overall survival.

NOTE Confidence: 0.938423890909091

00:29:36.950 --> 00:29:39.316 For Radian 4, this is the phase

NOTE Confidence: 0.938423890909091

00:29:39.316 --> 00:29:41.762 three study we did in lung

NOTE Confidence: 0.938423890909091

00:29:41.762 --> 00:29:44.026 and GI neuroendocrine tumors.

NOTE Confidence: 0.938423890909091

00:29:44.030 --> 00:29:47.405 Again patient were randomized to

NOTE Confidence: 0.938423890909091

00:29:47.405 --> 00:29:50.105 receive everolimus or placebo.

NOTE Confidence: 0.938423890909091

00:29:50.110 --> 00:29:54.148 The the the, the PFS improved from  
NOTE Confidence: 0.938423890909091

00:29:54.150 --> 00:29:56.590 3.9 months to 11 months with a  
NOTE Confidence: 0.938423890909091

00:29:56.590 --> 00:29:59.270 hazard ratio of 0.48 and a trend  
NOTE Confidence: 0.938423890909091

00:29:59.270 --> 00:30:01.270 to our overall survival benefit.  
NOTE Confidence: 0.9603804

00:30:04.990 --> 00:30:07.090 Another targeted agent that's  
NOTE Confidence: 0.9603804

00:30:07.090 --> 00:30:09.190 shown benefit is sunitip.  
NOTE Confidence: 0.9603804

00:30:09.190 --> 00:30:12.102 So Sunita was initially evaluated in a  
NOTE Confidence: 0.9603804

00:30:12.102 --> 00:30:15.427 phase two study being that had two cohorts  
NOTE Confidence: 0.9603804

00:30:15.430 --> 00:30:18.195 for intestinal neuroendocrine tumors and  
NOTE Confidence: 0.9603804

00:30:18.195 --> 00:30:19.944 for pancreatic neuroendocrine tumors.  
NOTE Confidence: 0.9603804

00:30:19.944 --> 00:30:22.730 All the responses were seen in the  
NOTE Confidence: 0.9603804

00:30:22.794 --> 00:30:24.669 pancreatic neuroendocrine group.  
NOTE Confidence: 0.9603804

00:30:24.670 --> 00:30:28.189 So it was taken into a phase three trial.  
NOTE Confidence: 0.9603804

00:30:28.190 --> 00:30:30.650 The study actually terminated early  
NOTE Confidence: 0.9603804

00:30:30.650 --> 00:30:33.110 at an unplanned interim analysis.  
NOTE Confidence: 0.9603804

00:30:33.110 --> 00:30:36.080 Nonetheless there it was significant

NOTE Confidence: 0.9603804

00:30:36.080 --> 00:30:39.448 benefit demonstrating PFS and then that

NOTE Confidence: 0.9603804

00:30:39.448 --> 00:30:42.790 led to the FDA approval of the drug

NOTE Confidence: 0.9603804

00:30:42.790 --> 00:30:46.750 for pancreatic neuroendocrine tumors.

NOTE Confidence: 0.9603804

00:30:46.750 --> 00:30:49.126 We do believe VEGF inhibitors may

NOTE Confidence: 0.9603804

00:30:49.126 --> 00:30:51.856 have a role in extra pancreatic

NOTE Confidence: 0.9603804

00:30:51.856 --> 00:30:54.148 neuroendocrine tumor as well.

NOTE Confidence: 0.9603804

00:30:54.150 --> 00:30:56.292 This is a another phase three trial

NOTE Confidence: 0.9603804

00:30:56.292 --> 00:30:58.547 that I did early in my career,

NOTE Confidence: 0.9603804

00:30:58.550 --> 00:31:01.174 the SWAG O 518.

NOTE Confidence: 0.9603804

00:31:01.174 --> 00:31:05.400 And the in this study patients were

NOTE Confidence: 0.9603804

00:31:05.400 --> 00:31:08.315 randomized from octreotype plus interferon

NOTE Confidence: 0.9603804

00:31:08.315 --> 00:31:11.190 versus octreotype plus Bebasus MAP.

NOTE Confidence: 0.9603804

00:31:11.190 --> 00:31:13.192 Where we're able to show in this

NOTE Confidence: 0.9603804

00:31:13.192 --> 00:31:15.374 study is that although the response

NOTE Confidence: 0.9603804

00:31:15.374 --> 00:31:18.398 rate improved with Bebasusan MAP and

NOTE Confidence: 0.9603804

00:31:18.398 --> 00:31:21.388 toxicity was better was Bebasusan map,  
NOTE Confidence: 0.9603804

00:31:21.390 --> 00:31:24.000 there was not any significant  
NOTE Confidence: 0.9603804

00:31:24.000 --> 00:31:26.610 difference in progression free survival.  
NOTE Confidence: 0.9603804

00:31:26.610 --> 00:31:28.110 So this is probably one of  
NOTE Confidence: 0.9603804

00:31:28.110 --> 00:31:29.570 my regrets in the career.  
NOTE Confidence: 0.9603804

00:31:29.570 --> 00:31:31.568 I probably should have done this  
NOTE Confidence: 0.9603804

00:31:31.568 --> 00:31:33.590 study against placebo and we would  
NOTE Confidence: 0.9603804

00:31:33.590 --> 00:31:36.136 have had had another drug available  
NOTE Confidence: 0.9603804

00:31:36.136 --> 00:31:40.366 for neuroendocrine much earlier on.  
NOTE Confidence: 0.9603804

00:31:40.370 --> 00:31:42.642 This is what the time point in my  
NOTE Confidence: 0.9603804

00:31:42.642 --> 00:31:44.659 career where we weren't sure whether  
NOTE Confidence: 0.9603804

00:31:44.659 --> 00:31:47.170 we can execute a placebo control trial.  
NOTE Confidence: 0.9603804

00:31:47.170 --> 00:31:49.290 It's certainly a little bit harder to do,  
NOTE Confidence: 0.9603804

00:31:49.290 --> 00:31:51.710 but often placebo control trial  
NOTE Confidence: 0.9603804

00:31:51.710 --> 00:31:53.646 give you cleaner data.  
NOTE Confidence: 0.9603804

00:31:53.650 --> 00:31:56.210 Especially when the comparator

NOTE Confidence: 0.9603804

00:31:56.210 --> 00:31:59.730 arm is not is not very carefully

NOTE Confidence: 0.9603804

00:31:59.730 --> 00:32:01.730 what is not well defined.

NOTE Confidence: 0.938576366666667

00:32:04.410 --> 00:32:08.375 So there has been others who evaluated

NOTE Confidence: 0.938576366666667

00:32:08.375 --> 00:32:11.770 veget inhibitors in your in the Contuber.

NOTE Confidence: 0.938576366666667

00:32:11.770 --> 00:32:13.810 This is a study conducted

NOTE Confidence: 0.938576366666667

00:32:13.810 --> 00:32:15.850 also in the cooperative group.

NOTE Confidence: 0.938576366666667

00:32:15.850 --> 00:32:18.750 The Pi is Emily Burksland and

NOTE Confidence: 0.938576366666667

00:32:18.750 --> 00:32:21.650 patient were randomly assigned to

NOTE Confidence: 0.938576366666667

00:32:21.650 --> 00:32:23.970 either pizopanit versus placebo.

NOTE Confidence: 0.938576366666667

00:32:23.970 --> 00:32:26.424 And there there was the benefit

NOTE Confidence: 0.938576366666667

00:32:26.424 --> 00:32:28.752 in terms of progression free

NOTE Confidence: 0.938576366666667

00:32:28.752 --> 00:32:31.812 survival also demonstrated in extra

NOTE Confidence: 0.938576366666667

00:32:31.812 --> 00:32:33.648 pancreatic neuroendocrine tumors.

NOTE Confidence: 0.938576366666667

00:32:33.650 --> 00:32:37.045 So potentially showing the importance

NOTE Confidence: 0.938576366666667

00:32:37.045 --> 00:32:41.309 of role of VEGF inhibitor outside

NOTE Confidence: 0.938576366666667

00:32:41.309 --> 00:32:45.380 beyond the pancreatic group in terms  
NOTE Confidence: 0.938576366666667

00:32:45.380 --> 00:32:48.868 of phase three studies for extra  
NOTE Confidence: 0.938576366666667

00:32:48.868 --> 00:32:51.442 pancreatic neuroendocrine tumor.  
NOTE Confidence: 0.938576366666667

00:32:51.442 --> 00:32:54.442 And there's also a study that was  
NOTE Confidence: 0.938576366666667

00:32:54.442 --> 00:32:56.708 performed in two studies that were  
NOTE Confidence: 0.938576366666667

00:32:56.708 --> 00:32:59.972 performing in China with Serofatin NIP,  
NOTE Confidence: 0.938576366666667

00:32:59.972 --> 00:33:03.120 another VEGF or multi kinase  
NOTE Confidence: 0.938576366666667

00:33:03.120 --> 00:33:04.860 inhibitor demonstrating similar  
NOTE Confidence: 0.938576366666667

00:33:04.860 --> 00:33:07.668 magnitude of benefit for Serofatin  
NOTE Confidence: 0.938576366666667

00:33:07.668 --> 00:33:11.084 Nip both in pancreatic net and extra  
NOTE Confidence: 0.938576366666667

00:33:11.084 --> 00:33:13.443 pancreatic net unfortunately the FDA.  
NOTE Confidence: 0.938576366666667

00:33:13.443 --> 00:33:15.748 It's going to probably require  
NOTE Confidence: 0.938576366666667

00:33:15.748 --> 00:33:18.718 the the company to redo the trial  
NOTE Confidence: 0.938576366666667

00:33:18.718 --> 00:33:21.614 because it did not contain it was a  
NOTE Confidence: 0.938576366666667

00:33:21.614 --> 00:33:23.748 purely Chinese population and the  
NOTE Confidence: 0.938576366666667

00:33:23.748 --> 00:33:26.058 population may not fully represent



NOTE Confidence: 0.938576366666667

00:33:26.058 --> 00:33:28.943 the lines of prior therapy Western

NOTE Confidence: 0.938576366666667

00:33:28.943 --> 00:33:31.580 populations would have been exposed to.

NOTE Confidence: 0.948080688888889

00:33:34.140 --> 00:33:36.348 Next I'm going to mention while

NOTE Confidence: 0.948080688888889

00:33:36.348 --> 00:33:38.592 Doctor Kunz's trial Ecog 2211,

NOTE Confidence: 0.948080688888889

00:33:38.592 --> 00:33:42.705 this is actually a very important trial.

NOTE Confidence: 0.948080688888889

00:33:42.705 --> 00:33:45.780 Partially because the initial development

NOTE Confidence: 0.948080688888889

00:33:45.780 --> 00:33:48.266 of Timosolomite were essentially

NOTE Confidence: 0.948080688888889

00:33:48.266 --> 00:33:52.230 skipped the single agent step they were,

NOTE Confidence: 0.948080688888889

00:33:52.230 --> 00:33:55.178 you know most of the trials that

NOTE Confidence: 0.948080688888889

00:33:55.178 --> 00:33:57.130 were published were doublets.

NOTE Confidence: 0.948080688888889

00:33:57.130 --> 00:33:59.426 So always been a question to feel

NOTE Confidence: 0.948080688888889

00:33:59.426 --> 00:34:01.329 that whether you need doublets

NOTE Confidence: 0.948080688888889

00:34:01.330 --> 00:34:04.928 or you know where the agent is,

NOTE Confidence: 0.948080688888889

00:34:04.930 --> 00:34:07.990 Timosolomite by itself is a sufficient.

NOTE Confidence: 0.948080688888889

00:34:07.990 --> 00:34:09.434 Certainly there's rationale to

NOTE Confidence: 0.948080688888889

00:34:09.434 --> 00:34:11.790 look at this class of agents in  
NOTE Confidence: 0.948080688888889

00:34:11.790 --> 00:34:13.270 pancreatic neuro in the consumers.  
NOTE Confidence: 0.948080688888889

00:34:13.270 --> 00:34:16.228 If you dig back into Chuck  
NOTE Confidence: 0.948080688888889

00:34:16.228 --> 00:34:18.910 Mattel's papers and so forth,  
NOTE Confidence: 0.948080688888889

00:34:18.910 --> 00:34:21.466 DTIC is active in the disease.  
NOTE Confidence: 0.948080688888889

00:34:21.470 --> 00:34:24.534 So this is a trial that compared Timosolomite  
NOTE Confidence: 0.948080688888889

00:34:24.534 --> 00:34:28.334 to Tim Cape at the intern analysis.  
NOTE Confidence: 0.948080688888889

00:34:28.334 --> 00:34:31.170 The study met its primary  
NOTE Confidence: 0.948080688888889

00:34:31.170 --> 00:34:33.170 endpoint and showed improvement  
NOTE Confidence: 0.948080688888889

00:34:33.170 --> 00:34:35.420 in progression free survival.  
NOTE Confidence: 0.948080688888889

00:34:35.420 --> 00:34:39.073 For our patients with Tim Kay and I  
NOTE Confidence: 0.948080688888889

00:34:39.073 --> 00:34:41.538 think another actually very important  
NOTE Confidence: 0.948080688888889

00:34:41.538 --> 00:34:44.729 finding from this study is the  
NOTE Confidence: 0.948080688888889

00:34:44.729 --> 00:34:47.009 prognostic and significance with  
NOTE Confidence: 0.948080688888889

00:34:47.009 --> 00:34:50.980 association of the MGMT expression  
NOTE Confidence: 0.948080688888889

00:34:50.980 --> 00:34:55.440 with the response in this is a

NOTE Confidence: 0.948080688888889

00:34:55.440 --> 00:34:58.508 DNA repair pathway when that often

NOTE Confidence: 0.948080688888889

00:34:58.508 --> 00:35:01.026 are methylated MGMT and leading

NOTE Confidence: 0.948080688888889

00:35:01.026 --> 00:35:03.287 to low expression and you can see.

NOTE Confidence: 0.948080688888889

00:35:03.290 --> 00:35:05.867 That for patients with low MGMT,

NOTE Confidence: 0.948080688888889

00:35:05.867 --> 00:35:08.786 the response rate is much higher than

NOTE Confidence: 0.948080688888889

00:35:08.786 --> 00:35:11.490 those who have intact MGMT expression.

NOTE Confidence: 0.938019439166666

00:35:13.530 --> 00:35:15.746 So if you look at the current treatment

NOTE Confidence: 0.938019439166666

00:35:15.746 --> 00:35:17.450 landscape for neuroendocrine tumor,

NOTE Confidence: 0.938019439166666

00:35:17.450 --> 00:35:19.886 we have come a long way.

NOTE Confidence: 0.938019439166666

00:35:19.890 --> 00:35:22.361 You know in the beginning historically we

NOTE Confidence: 0.938019439166666

00:35:22.361 --> 00:35:25.089 only have one agent for pancreatic net.

NOTE Confidence: 0.938019439166666

00:35:25.090 --> 00:35:28.324 Now you have number of phase three

NOTE Confidence: 0.938019439166666

00:35:28.324 --> 00:35:31.203 clinical trial covering many of the

NOTE Confidence: 0.938019439166666

00:35:31.203 --> 00:35:33.543 different in your endocrine tumors.

NOTE Confidence: 0.938019439166666

00:35:33.550 --> 00:35:36.494 Essentially these are clustered

NOTE Confidence: 0.938019439166666

00:35:36.494 --> 00:35:39.218 around agents that targets these.  
NOTE Confidence: 0.938019439166666

00:35:39.218 --> 00:35:42.382 These are stable or early disease like  
NOTE Confidence: 0.938019439166666

00:35:42.382 --> 00:35:45.263 TRILTY and then Realty in the pro  
NOTE Confidence: 0.938019439166666

00:35:45.263 --> 00:35:48.896 Med and the CLARINET study and in the  
NOTE Confidence: 0.938019439166666

00:35:48.896 --> 00:35:52.433 studies who tend to target patients  
NOTE Confidence: 0.938019439166666

00:35:52.433 --> 00:35:55.464 was faster progressing disease PRT  
NOTE Confidence: 0.938019439166666

00:35:55.464 --> 00:35:57.588 somewhere in the middle that required  
NOTE Confidence: 0.938019439166666

00:35:57.588 --> 00:35:59.720 progression in the past three years.  
NOTE Confidence: 0.938019439166666

00:35:59.720 --> 00:36:02.246 And most of the targeted agents  
NOTE Confidence: 0.938019439166666

00:36:02.246 --> 00:36:04.615 require progression in the past one  
NOTE Confidence: 0.938019439166666

00:36:04.615 --> 00:36:07.055 year when in the case of Radian 4  
NOTE Confidence: 0.938019439166666

00:36:07.128 --> 00:36:09.960 progression within the past six months.  
NOTE Confidence: 0.938019439166666

00:36:09.960 --> 00:36:12.592 So what are some of the remaining  
NOTE Confidence: 0.938019439166666

00:36:12.592 --> 00:36:14.412 challenges and questions that we  
NOTE Confidence: 0.938019439166666

00:36:14.412 --> 00:36:16.589 we have when you're in the current  
NOTE Confidence: 0.938019439166666

00:36:16.589 --> 00:36:17.880 tumor at this point,

NOTE Confidence: 0.938019439166666  
00:36:17.880 --> 00:36:20.288 one of the question I get asked  
NOTE Confidence: 0.938019439166666  
00:36:20.288 --> 00:36:22.280 the most is sequencing,  
NOTE Confidence: 0.938019439166666  
00:36:22.280 --> 00:36:24.805 what's the optimal sequencing of  
NOTE Confidence: 0.938019439166666  
00:36:24.805 --> 00:36:28.749 therapy for neuro in the current tumors?  
NOTE Confidence: 0.938019439166666  
00:36:28.750 --> 00:36:30.670 So it's kind of interesting  
NOTE Confidence: 0.938019439166666  
00:36:30.670 --> 00:36:32.590 because you're in the consumers,  
NOTE Confidence: 0.938019439166666  
00:36:32.590 --> 00:36:35.082 you had approval a lot of agents  
NOTE Confidence: 0.938019439166666  
00:36:35.082 --> 00:36:38.386 while in a short period span of time.  
NOTE Confidence: 0.938019439166666  
00:36:38.390 --> 00:36:41.518 So they were not really developing a way  
NOTE Confidence: 0.938019439166666  
00:36:41.518 --> 00:36:44.070 where they were specific align first line,  
NOTE Confidence: 0.938019439166666  
00:36:44.070 --> 00:36:45.938 second line, third line.  
NOTE Confidence: 0.938019439166666  
00:36:45.938 --> 00:36:48.740 Most the drugs were either approved  
NOTE Confidence: 0.938019439166666  
00:36:48.821 --> 00:36:51.271 for progressive disease or they  
NOTE Confidence: 0.938019439166666  
00:36:51.271 --> 00:36:53.721 were just approved for advanced  
NOTE Confidence: 0.938019439166666  
00:36:53.805 --> 00:36:56.012 disease but optimal sequencing.  
NOTE Confidence: 0.938019439166666

00:36:56.012 --> 00:36:59.336 It's really talking about which sequence  
NOTE Confidence: 0.938019439166666

00:36:59.336 --> 00:37:02.990 leads to the best overall longterm survival.  
NOTE Confidence: 0.938019439166666

00:37:02.990 --> 00:37:05.450 This is actually extremely  
NOTE Confidence: 0.938019439166666

00:37:05.450 --> 00:37:07.910 difficult question to answer.  
NOTE Confidence: 0.938019439166666

00:37:07.910 --> 00:37:11.180 It's not about which agent when used  
NOTE Confidence: 0.938019439166666

00:37:11.180 --> 00:37:13.670 first has the longest initial PFS,  
NOTE Confidence: 0.938019439166666

00:37:13.670 --> 00:37:15.694 because if that agent,  
NOTE Confidence: 0.938019439166666

00:37:15.694 --> 00:37:16.706 you know,  
NOTE Confidence: 0.938019439166666

00:37:16.710 --> 00:37:21.006 essentially takes out your kidney or makes  
NOTE Confidence: 0.938019439166666

00:37:21.006 --> 00:37:23.638 it difficult for you receive other agents.  
NOTE Confidence: 0.938019439166666

00:37:23.640 --> 00:37:26.136 And it may not be the best agent  
NOTE Confidence: 0.938019439166666

00:37:26.136 --> 00:37:27.640 to use initially.  
NOTE Confidence: 0.938019439166666

00:37:27.640 --> 00:37:29.649 So almost certainly this is if you  
NOTE Confidence: 0.938019439166666

00:37:29.649 --> 00:37:31.800 really want to answer this question,  
NOTE Confidence: 0.938019439166666

00:37:31.800 --> 00:37:35.440 it needs overall survival endpoint.  
NOTE Confidence: 0.938019439166666

00:37:35.440 --> 00:37:35.949 Well,

NOTE Confidence: 0.938019439166666  
00:37:35.949 --> 00:37:39.003 here's the challenge right when for  
NOTE Confidence: 0.938019439166666  
00:37:39.003 --> 00:37:41.526 different indications you have different  
NOTE Confidence: 0.938019439166666  
00:37:41.526 --> 00:37:44.840 number of treatments available,  
NOTE Confidence: 0.938019439166666  
00:37:44.840 --> 00:37:46.640 the approved therapy for lung,  
NOTE Confidence: 0.938019439166666  
00:37:46.640 --> 00:37:49.118 there's only ever limus in peanut you  
NOTE Confidence: 0.938019439166666  
00:37:49.118 --> 00:37:51.519 have six agents that are available,  
NOTE Confidence: 0.938019439166666  
00:37:51.520 --> 00:37:53.728 approved you can use.  
NOTE Confidence: 0.938019439166666  
00:37:53.728 --> 00:37:56.488 A 7th agents demonstrated activity  
NOTE Confidence: 0.938019439166666  
00:37:56.490 --> 00:38:00.330 that that's probably works well.  
NOTE Confidence: 0.938019439166666  
00:38:00.330 --> 00:38:03.750 You can imagine trying to compare  
NOTE Confidence: 0.938019439166666  
00:38:03.750 --> 00:38:04.890 optimal sequences.  
NOTE Confidence: 0.938019439166666  
00:38:04.890 --> 00:38:08.810 There's 5040 sequences,  
NOTE Confidence: 0.938019439166666  
00:38:08.810 --> 00:38:11.930 5040 arms for overall survival.  
NOTE Confidence: 0.938019439166666  
00:38:11.930 --> 00:38:14.458 This is not where we want to spend  
NOTE Confidence: 0.938019439166666  
00:38:14.458 --> 00:38:16.846 our energy and because I think  
NOTE Confidence: 0.938019439166666

00:38:16.846 --> 00:38:19.480 likely before evening to solve a  
NOTE Confidence: 0.938019439166666

00:38:19.571 --> 00:38:22.696 simpler question before you actually.  
NOTE Confidence: 0.938019439166666

00:38:22.700 --> 00:38:24.860 To answer the question and complete a trial,  
NOTE Confidence: 0.938019439166666

00:38:24.860 --> 00:38:26.196 the treatment landscape would  
NOTE Confidence: 0.938019439166666

00:38:26.196 --> 00:38:28.200 have changed in the trial design  
NOTE Confidence: 0.938019439166666

00:38:28.258 --> 00:38:30.180 will probably no longer be valid.  
NOTE Confidence: 0.938423890909091

00:38:32.540 --> 00:38:34.370 And to give a actually example  
NOTE Confidence: 0.938423890909091

00:38:34.370 --> 00:38:35.980 of attempt to do this,  
NOTE Confidence: 0.938423890909091

00:38:35.980 --> 00:38:38.122 our European colleague  
NOTE Confidence: 0.938423890909091

00:38:38.122 --> 00:38:40.978 contacted the secretor trial.  
NOTE Confidence: 0.938423890909091

00:38:40.980 --> 00:38:43.536 The secretor trial look look to  
NOTE Confidence: 0.938423890909091

00:38:43.536 --> 00:38:46.362 compare the sequence of Ever Linus  
NOTE Confidence: 0.938423890909091

00:38:46.362 --> 00:38:48.418 followed by Streptozosin based  
NOTE Confidence: 0.938423890909091

00:38:48.418 --> 00:38:50.531 chemotherapy or Streptozosin based  
NOTE Confidence: 0.938423890909091

00:38:50.531 --> 00:38:52.996 chemotherapy followed by ever Linus.  
NOTE Confidence: 0.938423890909091

00:38:53.000 --> 00:38:55.800 They weren't going to be quite ambitious



NOTE Confidence: 0.938423890909091  
00:38:55.800 --> 00:38:58.480 to try OS as the primary endpoint.  
NOTE Confidence: 0.938423890909091  
00:38:58.480 --> 00:39:00.960 They were going to look at P FS2.  
NOTE Confidence: 0.938423890909091  
00:39:00.960 --> 00:39:04.824 So initially are due to a cruel  
NOTE Confidence: 0.938423890909091  
00:39:04.824 --> 00:39:08.008 issues that they had to do scale  
NOTE Confidence: 0.938423890909091  
00:39:08.008 --> 00:39:10.216 back their ambitions to look at  
NOTE Confidence: 0.938423890909091  
00:39:10.216 --> 00:39:13.080 P FS1 as the primary endpoint.  
NOTE Confidence: 0.938423890909091  
00:39:13.080 --> 00:39:15.996 So what did the study show?  
NOTE Confidence: 0.938423890909091  
00:39:16.000 --> 00:39:18.775 Yeah, actually showed that although  
NOTE Confidence: 0.938423890909091  
00:39:18.775 --> 00:39:21.550 Streptozosin set of toxic chemotherapy.  
NOTE Confidence: 0.938423890909091  
00:39:21.550 --> 00:39:23.790 Was a little bit more toxic but higher,  
NOTE Confidence: 0.938423890909091  
00:39:23.790 --> 00:39:25.710 had a higher response rate,  
NOTE Confidence: 0.938423890909091  
00:39:25.710 --> 00:39:28.650 but there was no difference in progression  
NOTE Confidence: 0.938423890909091  
00:39:28.650 --> 00:39:30.829 free survival between the two arms.  
NOTE Confidence: 0.938423890909091  
00:39:30.830 --> 00:39:34.400 So higher higher response rate may not  
NOTE Confidence: 0.938423890909091  
00:39:34.400 --> 00:39:38.150 necessarily lead to a better outcome.  
NOTE Confidence: 0.938423890909091

00:39:38.150 --> 00:39:40.845 The second most frequent question I get  
NOTE Confidence: 0.938423890909091

00:39:40.845 --> 00:39:43.412 asked about nearing the consumer these  
NOTE Confidence: 0.938423890909091

00:39:43.412 --> 00:39:46.106 days is precision medicines and biomarkers.  
NOTE Confidence: 0.938423890909091

00:39:46.110 --> 00:39:48.710 If you did a search on your end,  
NOTE Confidence: 0.938423890909091

00:39:48.710 --> 00:39:51.755 the consumer and biomarkers on Pub Med.  
NOTE Confidence: 0.938423890909091

00:39:51.760 --> 00:39:54.204 And you'll get thousands,  
NOTE Confidence: 0.938423890909091

00:39:54.204 --> 00:39:57.016 probably near 10,000 results back.  
NOTE Confidence: 0.938423890909091

00:39:57.016 --> 00:40:00.432 So what do we know about biomarkers  
NOTE Confidence: 0.938423890909091

00:40:00.432 --> 00:40:03.040 for neuroendocrine tumors?  
NOTE Confidence: 0.938423890909091

00:40:03.040 --> 00:40:04.715 I usually think about biomarkers  
NOTE Confidence: 0.938423890909091

00:40:04.715 --> 00:40:05.720 as two classes.  
NOTE Confidence: 0.938423890909091

00:40:05.720 --> 00:40:07.760 These are prognostic identifying  
NOTE Confidence: 0.938423890909091

00:40:07.760 --> 00:40:10.696 those people who have a better  
NOTE Confidence: 0.938423890909091

00:40:10.696 --> 00:40:13.284 or worse outcome and predictive  
NOTE Confidence: 0.938423890909091

00:40:13.284 --> 00:40:16.394 meaning to actually sorting out  
NOTE Confidence: 0.938423890909091

00:40:16.400 --> 00:40:18.890 individual who are more likely.

NOTE Confidence: 0.938423890909091

00:40:18.890 --> 00:40:21.116 But then similar individual without a

NOTE Confidence: 0.938423890909091

00:40:21.116 --> 00:40:23.230 biomarker to experience a favorable

NOTE Confidence: 0.938423890909091

00:40:23.230 --> 00:40:25.842 unfavorable benefit from an exposure to

NOTE Confidence: 0.938423890909091

00:40:25.842 --> 00:40:28.050 a medical product we environment agents.

NOTE Confidence: 0.938423890909091

00:40:28.050 --> 00:40:31.106 So the bottom line is who should get

NOTE Confidence: 0.938423890909091

00:40:31.106 --> 00:40:34.117 this treatment is really the important

NOTE Confidence: 0.938423890909091

00:40:34.117 --> 00:40:36.289 question for predictive biomarker.

NOTE Confidence: 0.938423890909091

00:40:36.290 --> 00:40:39.419 Another way to think about the importance

NOTE Confidence: 0.938423890909091

00:40:39.419 --> 00:40:41.663 of predictive biomarker is really

NOTE Confidence: 0.938423890909091

00:40:41.663 --> 00:40:44.178 thinking about like who's going to

NOTE Confidence: 0.938423890909091

00:40:44.178 --> 00:40:47.494 benefit from treatment if you have a

NOTE Confidence: 0.938423890909091

00:40:47.494 --> 00:40:49.538 treatment where everybody benefits.

NOTE Confidence: 0.938423890909091

00:40:49.540 --> 00:40:52.180 Predictive biomarker can almost becomes

NOTE Confidence: 0.938423890909091

00:40:52.180 --> 00:40:54.292 essentially a prognostic biomarker.

NOTE Confidence: 0.938423890909091

00:40:54.300 --> 00:40:57.530 It's probably of less clinical

NOTE Confidence: 0.938423890909091

00:40:57.530 --> 00:41:00.028 importance in the situation where  
NOTE Confidence: 0.938423890909091

00:41:00.028 --> 00:41:02.338 half the patient will benefit.  
NOTE Confidence: 0.938423890909091

00:41:02.340 --> 00:41:05.778 A predictive biomarker is super useful  
NOTE Confidence: 0.938423890909091

00:41:05.780 --> 00:41:08.125 and it's even more important when a  
NOTE Confidence: 0.938423890909091

00:41:08.125 --> 00:41:10.655 smaller group of patient have profound  
NOTE Confidence: 0.938423890909091

00:41:10.655 --> 00:41:13.668 benefit, but most people don't.  
NOTE Confidence: 0.938423890909091

00:41:13.670 --> 00:41:15.764 So what is actually the situation  
NOTE Confidence: 0.938423890909091

00:41:15.764 --> 00:41:18.235 you are in different tumor which of  
NOTE Confidence: 0.938423890909091

00:41:18.235 --> 00:41:20.587 these waterfall plot do we look like?  
NOTE Confidence: 0.938423890909091

00:41:20.590 --> 00:41:23.374 Fortunately it looks like this whereas  
NOTE Confidence: 0.938423890909091

00:41:23.374 --> 00:41:27.690 a most the patients benefiting from the  
NOTE Confidence: 0.938423890909091

00:41:27.690 --> 00:41:30.990 treatment within their treatment indications.  
NOTE Confidence: 0.9534618125

00:41:34.390 --> 00:41:36.520 So the challenge of predictive  
NOTE Confidence: 0.9534618125

00:41:36.520 --> 00:41:39.154 biomarker is essentially you have to  
NOTE Confidence: 0.9534618125

00:41:39.154 --> 00:41:41.319 randomize more patient all patients.  
NOTE Confidence: 0.9534618125

00:41:41.320 --> 00:41:43.890 Including patients who doesn't have

NOTE Confidence: 0.9534618125

00:41:43.890 --> 00:41:46.489 the biomarker because without that

NOTE Confidence: 0.9534618125

00:41:46.489 --> 00:41:49.104 randomization is very difficult to

NOTE Confidence: 0.9534618125

00:41:49.104 --> 00:41:51.652 understand which biomarker is important.

NOTE Confidence: 0.9534618125

00:41:51.652 --> 00:41:54.354 You should do this when the marker

NOTE Confidence: 0.9534618125

00:41:54.354 --> 00:41:57.474 is suspected to be predictive but not

NOTE Confidence: 0.9534618125

00:41:57.474 --> 00:42:00.405 proven and you have reliable assay

NOTE Confidence: 0.9534618125

00:42:00.405 --> 00:42:03.488 methodology and cut points and there's

NOTE Confidence: 0.9534618125

00:42:03.488 --> 00:42:06.040 reason to expect benefit potentially

NOTE Confidence: 0.9534618125

00:42:06.040 --> 00:42:07.880 in biomarker negative patients.

NOTE Confidence: 0.937143952413793

00:42:11.310 --> 00:42:14.264 Much more common we seeing oncology these

NOTE Confidence: 0.937143952413793

00:42:14.264 --> 00:42:17.829 days is this approach which is establishing

NOTE Confidence: 0.937143952413793

00:42:17.829 --> 00:42:21.159 a efficacy of biomarker population which

NOTE Confidence: 0.937143952413793

00:42:21.238 --> 00:42:24.278 means we only essentially randomize

NOTE Confidence: 0.937143952413793

00:42:24.278 --> 00:42:26.710 the biomarker positive population.

NOTE Confidence: 0.937143952413793

00:42:26.710 --> 00:42:30.438 So here you can prove the biomarker positive

NOTE Confidence: 0.937143952413793

00:42:30.438 --> 00:42:33.590 benefit patients benefit from new treatment.  
NOTE Confidence: 0.937143952413793

00:42:33.590 --> 00:42:36.310 But it's best used when no benefit is  
NOTE Confidence: 0.937143952413793

00:42:36.310 --> 00:42:39.348 expected in bowel marker negative population.  
NOTE Confidence: 0.937143952413793

00:42:39.350 --> 00:42:41.426 You don't have any information gained  
NOTE Confidence: 0.937143952413793

00:42:41.426 --> 00:42:44.030 about the bowel marker negative population.  
NOTE Confidence: 0.941691228571429

00:42:46.670 --> 00:42:48.975 But often sometimes we get it wrong, right.  
NOTE Confidence: 0.941691228571429

00:42:48.975 --> 00:42:52.230 We we don't initially fully understand this.  
NOTE Confidence: 0.941691228571429

00:42:52.230 --> 00:42:54.490 The classic example in  
NOTE Confidence: 0.941691228571429

00:42:54.490 --> 00:42:56.750 colon cancer is cetuximab.  
NOTE Confidence: 0.941691228571429

00:42:56.750 --> 00:42:58.895 The initial FDA approval in  
NOTE Confidence: 0.941691228571429

00:42:58.895 --> 00:43:01.040 clinical trial was for patients.  
NOTE Confidence: 0.941691228571429

00:43:01.040 --> 00:43:05.720 Who had e.g. Fr expression on I HC?  
NOTE Confidence: 0.941691228571429

00:43:05.720 --> 00:43:08.023 Turns out that has nothing to do  
NOTE Confidence: 0.941691228571429

00:43:08.023 --> 00:43:09.879 with whether someone benefits from  
NOTE Confidence: 0.941691228571429

00:43:09.880 --> 00:43:13.516 situximab or not in colorectal cancer.  
NOTE Confidence: 0.941691228571429

00:43:13.520 --> 00:43:16.355 And the net example is really kind

NOTE Confidence: 0.941691228571429  
00:43:16.355 --> 00:43:19.000 something I kind of lived through.  
NOTE Confidence: 0.941691228571429  
00:43:19.000 --> 00:43:21.275 After we started a phase three trial,  
NOTE Confidence: 0.941691228571429  
00:43:21.280 --> 00:43:23.476 a publication came out in science  
NOTE Confidence: 0.941691228571429  
00:43:23.480 --> 00:43:26.756 showing about 15% of the patients with  
NOTE Confidence: 0.941691228571429  
00:43:26.756 --> 00:43:30.248 pancreatic net at M Tor pathway mutations.  
NOTE Confidence: 0.941691228571429  
00:43:30.250 --> 00:43:32.170 So I I I will,  
NOTE Confidence: 0.941691228571429  
00:43:32.170 --> 00:43:35.014 I would gladly admit I was a very lucky  
NOTE Confidence: 0.941691228571429  
00:43:35.014 --> 00:43:38.203 not to know that when I started the trial.  
NOTE Confidence: 0.941691228571429  
00:43:38.210 --> 00:43:41.586 But because it turns out you  
NOTE Confidence: 0.941691228571429  
00:43:41.586 --> 00:43:43.730 know extra pancreatic net,  
NOTE Confidence: 0.941691228571429  
00:43:43.730 --> 00:43:45.530 none of the patients have  
NOTE Confidence: 0.941691228571429  
00:43:45.530 --> 00:43:46.610 mtor pathway mutations,  
NOTE Confidence: 0.941691228571429  
00:43:46.610 --> 00:43:48.686 quote mtor pathway mutations,  
NOTE Confidence: 0.941691228571429  
00:43:48.686 --> 00:43:52.490 but they all benefited from the therapy  
NOTE Confidence: 0.941691228571429  
00:43:52.490 --> 00:43:55.325 and even in the pancreatic net group  
NOTE Confidence: 0.941691228571429

00:43:55.330 --> 00:43:58.240 those who had mtor pathway mutations.  
NOTE Confidence: 0.941691228571429

00:43:58.240 --> 00:44:01.257 And didn't have M Tor pathway mutation  
NOTE Confidence: 0.941691228571429

00:44:01.257 --> 00:44:03.400 have similar magnitude of benefit.  
NOTE Confidence: 0.941691228571429

00:44:03.400 --> 00:44:06.438 That's not to say that it's not  
NOTE Confidence: 0.941691228571429

00:44:06.440 --> 00:44:08.762 correct that you know what what  
NOTE Confidence: 0.941691228571429

00:44:08.762 --> 00:44:11.121 was published is just means that  
NOTE Confidence: 0.941691228571429

00:44:11.121 --> 00:44:13.311 I don't think we may sometimes  
NOTE Confidence: 0.941691228571429

00:44:13.311 --> 00:44:15.866 know the full M Tor pathway or  
NOTE Confidence: 0.941691228571429

00:44:15.866 --> 00:44:17.996 how these drugs actually work.  
NOTE Confidence: 0

00:44:20.980 --> 00:44:23.020 Those are biomarkers.  
NOTE Confidence: 0

00:44:23.020 --> 00:44:25.060 In neuroendocrine trials,  
NOTE Confidence: 0

00:44:25.060 --> 00:44:28.420 the question often is asked about the  
NOTE Confidence: 0

00:44:28.420 --> 00:44:31.795 semester and syntacriphy in for semester.  
NOTE Confidence: 0

00:44:31.795 --> 00:44:35.020 And like octreotide and Realty,  
NOTE Confidence: 0

00:44:35.020 --> 00:44:37.440 the prominence study actually  
NOTE Confidence: 0

00:44:37.440 --> 00:44:41.216 allowed for both semester and



NOTE Confidence: 0

00:44:41.216 --> 00:44:45.284 receptor syntacrification of.

NOTE Confidence: 0

00:44:45.284 --> 00:44:53.420 And clarinet study only treated patient

NOTE Confidence: 0

00:44:53.612 --> 00:44:55.610 for semester and receptor positive.

NOTE Confidence: 0.943913018181818

00:44:57.930 --> 00:45:00.639 This one comes close to a predictive

NOTE Confidence: 0.943913018181818

00:45:00.639 --> 00:45:03.270 biomarker which is the degree of

NOTE Confidence: 0.943913018181818

00:45:03.270 --> 00:45:06.220 uptake and response and tumor

NOTE Confidence: 0.943913018181818

00:45:06.220 --> 00:45:09.730 shrinkage in in in for treatment

NOTE Confidence: 0.943913018181818

00:45:09.730 --> 00:45:12.650 with a peptide receptor radiotherapy

NOTE Confidence: 0.943913018181818

00:45:12.650 --> 00:45:14.732 as you can see that comparing

NOTE Confidence: 0.943913018181818

00:45:14.732 --> 00:45:17.260 to the using the craning scale.

NOTE Confidence: 0.943913018181818

00:45:17.260 --> 00:45:18.700 As the expression goes up,

NOTE Confidence: 0.943913018181818

00:45:18.700 --> 00:45:21.855 the response rate increase compared

NOTE Confidence: 0.943913018181818

00:45:21.855 --> 00:45:24.379 for peptide receptor radiotherapy.

NOTE Confidence: 0.957025933333333

00:45:26.420 --> 00:45:29.738 Another biomarker that was evaluated is

NOTE Confidence: 0.957025933333333

00:45:29.740 --> 00:45:33.580 is more like a pharmacodynamic biomarker.

NOTE Confidence: 0.957025933333333

00:45:33.580 --> 00:45:36.023 In early studies and single arm study  
NOTE Confidence: 0.9570259333333333

00:45:36.023 --> 00:45:39.006 it looked like those patient who had an  
NOTE Confidence: 0.9570259333333333

00:45:39.006 --> 00:45:42.444 early drop in pomegranate had a benefit  
NOTE Confidence: 0.9570259333333333

00:45:42.444 --> 00:45:44.940 for patients treated was everolimus.  
NOTE Confidence: 0.9570259333333333

00:45:44.940 --> 00:45:48.119 But this turned out actually not to be  
NOTE Confidence: 0.9570259333333333

00:45:48.119 --> 00:45:50.559 that useful when we took it to phase  
NOTE Confidence: 0.9570259333333333

00:45:50.559 --> 00:45:52.290 three because the placebo patient  
NOTE Confidence: 0.9570259333333333

00:45:52.290 --> 00:45:54.889 who had a 30% dropping from Granny  
NOTE Confidence: 0.9570259333333333

00:45:54.889 --> 00:45:58.110 A also had a better outcome as well.  
NOTE Confidence: 0.9570259333333333

00:45:58.110 --> 00:46:00.735 So likely this is pointing out some  
NOTE Confidence: 0.9570259333333333

00:46:00.735 --> 00:46:03.502 issues with the assay performance and  
NOTE Confidence: 0.9570259333333333

00:46:03.502 --> 00:46:05.374 also whether we're not you actually  
NOTE Confidence: 0.9570259333333333

00:46:05.374 --> 00:46:07.504 have to test these patient multiple  
NOTE Confidence: 0.9570259333333333

00:46:07.504 --> 00:46:10.150 times before you get a reliable results.  
NOTE Confidence: 0.9452853

00:46:12.320 --> 00:46:14.450 Another BOW marker attempting to look  
NOTE Confidence: 0.9452853

00:46:14.450 --> 00:46:17.542 at the predictive bow marker in terms of

NOTE Confidence: 0.9452853

00:46:17.542 --> 00:46:20.609 response is looking at profusion CT in

NOTE Confidence: 0.9452853

00:46:20.609 --> 00:46:22.954 patients treated with veg inhibitors.

NOTE Confidence: 0.9452853

00:46:22.960 --> 00:46:25.920 We're able to show that in patients treated

NOTE Confidence: 0.9452853

00:46:25.920 --> 00:46:28.574 with Bebasusan app is open in a flipper

NOTE Confidence: 0.9452853

00:46:28.574 --> 00:46:31.200 set that essentially baseline parameter

NOTE Confidence: 0.9452853

00:46:31.200 --> 00:46:33.994 and change after treatment correlated

NOTE Confidence: 0.9452853

00:46:33.994 --> 00:46:37.078 with the degree of tumor shrinkage.

NOTE Confidence: 0.9452853

00:46:37.080 --> 00:46:39.720 I think what we learned here is that

NOTE Confidence: 0.9452853

00:46:39.720 --> 00:46:41.957 these are very difficult to do.

NOTE Confidence: 0.9452853

00:46:41.960 --> 00:46:43.636 And very operator dependent.

NOTE Confidence: 0.9452853

00:46:43.636 --> 00:46:46.996 So it's was possible to do it in

NOTE Confidence: 0.9452853

00:46:46.996 --> 00:46:50.080 clinical trial taking it out to the

NOTE Confidence: 0.9452853

00:46:50.080 --> 00:46:52.400 wider clinical practice is challenging.

NOTE Confidence: 0.9452853

00:46:52.400 --> 00:46:55.039 So if you look at a biomarker

NOTE Confidence: 0.9452853

00:46:55.040 --> 00:46:57.188 landscape for neuroendocrine tumor,

NOTE Confidence: 0.9452853

00:46:57.188 --> 00:47:00.976 you see that in terms of understanding

NOTE Confidence: 0.9452853

00:47:00.976 --> 00:47:04.758 whether the treatment work in the in,

NOTE Confidence: 0.9452853

00:47:04.758 --> 00:47:08.384 in the indication we do pretty well.

NOTE Confidence: 0.9452853

00:47:08.390 --> 00:47:10.058 Whereas predictive biomarkers,

NOTE Confidence: 0.9452853

00:47:10.058 --> 00:47:13.394 there are a few promising ones

NOTE Confidence: 0.9452853

00:47:13.394 --> 00:47:15.348 like printing scale for

NOTE Confidence: 0.879102842222222

00:47:17.910 --> 00:47:19.656 PRT&M&MGMT for Timosolemai,

NOTE Confidence: 0.879102842222222

00:47:19.656 --> 00:47:23.148 However, we're still need a lot,

NOTE Confidence: 0.879102842222222

00:47:23.150 --> 00:47:25.606 lot more work to do in terms of

NOTE Confidence: 0.879102842222222

00:47:25.606 --> 00:47:29.880 getting real predictive biomarkers.

NOTE Confidence: 0.879102842222222

00:47:29.880 --> 00:47:31.668 So I mentioned earlier that we

NOTE Confidence: 0.879102842222222

00:47:31.668 --> 00:47:33.716 have a lot of approved therapy

NOTE Confidence: 0.879102842222222

00:47:33.716 --> 00:47:36.467 but most of these trial were not

NOTE Confidence: 0.879102842222222

00:47:36.467 --> 00:47:38.760 designed to ask a survival question.

NOTE Confidence: 0.879102842222222

00:47:38.760 --> 00:47:42.000 So you know has all this work been

NOTE Confidence: 0.879102842222222

00:47:42.000 --> 00:47:44.798 approval our patients doing better,

NOTE Confidence: 0.879102842222222

00:47:44.800 --> 00:47:47.411 we can look back into the SEAR

NOTE Confidence: 0.879102842222222

00:47:47.411 --> 00:47:49.071 database again and showing

NOTE Confidence: 0.879102842222222

00:47:49.071 --> 00:47:51.356 that the trend in improving,

NOTE Confidence: 0.879102842222222

00:47:51.360 --> 00:47:53.068 improving overall survival in

NOTE Confidence: 0.879102842222222

00:47:53.068 --> 00:47:55.630 patients with great one to two

NOTE Confidence: 0.879102842222222

00:47:55.708 --> 00:47:58.060 metastatic neuroendocrine tumors.

NOTE Confidence: 0.879102842222222

00:47:58.060 --> 00:48:01.066 Suggesting that what we did actually

NOTE Confidence: 0.879102842222222

00:48:01.066 --> 00:48:04.220 does actually make a real impact.

NOTE Confidence: 0.879102842222222

00:48:04.220 --> 00:48:06.476 So next what do you think we need

NOTE Confidence: 0.879102842222222

00:48:06.476 --> 00:48:08.926 to do to continue the progress

NOTE Confidence: 0.879102842222222

00:48:08.926 --> 00:48:10.734 in your endocrine tumors?

NOTE Confidence: 0.879102842222222

00:48:10.740 --> 00:48:12.930 I think clearly we one thing

NOTE Confidence: 0.879102842222222

00:48:12.930 --> 00:48:16.068 we learned is the use of robust

NOTE Confidence: 0.879102842222222

00:48:16.068 --> 00:48:18.398 randomized clinical trials and we

NOTE Confidence: 0.879102842222222

00:48:18.398 --> 00:48:20.612 shouldn't be shy about using placebo

NOTE Confidence: 0.879102842222222

00:48:20.612 --> 00:48:22.779 control trial in the right setting.  
NOTE Confidence: 0.8791028422222222

00:48:22.780 --> 00:48:25.195 We do need better availability of neuro  
NOTE Confidence: 0.8791028422222222

00:48:25.195 --> 00:48:28.089 in the model for translational research.  
NOTE Confidence: 0.8791028422222222

00:48:28.090 --> 00:48:30.658 I think we have a baseline group of  
NOTE Confidence: 0.8791028422222222

00:48:30.658 --> 00:48:33.203 therapy that works now to find the  
NOTE Confidence: 0.8791028422222222

00:48:33.203 --> 00:48:36.254 next pathway to target the next target.  
NOTE Confidence: 0.8791028422222222

00:48:36.254 --> 00:48:39.489 I think the the neuron models in  
NOTE Confidence: 0.8791028422222222

00:48:39.489 --> 00:48:42.207 the lab will really benefit us  
NOTE Confidence: 0.8791028422222222

00:48:42.210 --> 00:48:45.726 and we need to obviously explore  
NOTE Confidence: 0.8791028422222222

00:48:45.726 --> 00:48:47.484 novel therapeutic approaches.  
NOTE Confidence: 0.8791028422222222

00:48:47.490 --> 00:48:50.418 I'll just have two more slides  
NOTE Confidence: 0.8791028422222222

00:48:50.418 --> 00:48:52.760 on the modeling part so.  
NOTE Confidence: 0.8791028422222222

00:48:52.760 --> 00:48:54.710 There's a real challenge with  
NOTE Confidence: 0.8791028422222222

00:48:54.710 --> 00:48:56.270 developing models for well  
NOTE Confidence: 0.8791028422222222

00:48:56.338 --> 00:48:58.810 differentiating your endocrine tumors.  
NOTE Confidence: 0.8791028422222222

00:48:58.810 --> 00:49:01.630 There's been many attempt to generate

NOTE Confidence: 0.879102842222222

00:49:01.630 --> 00:49:03.983 cell lines, xenographs and organize.

NOTE Confidence: 0.879102842222222

00:49:03.983 --> 00:49:06.809 Principally they are limited by a

NOTE Confidence: 0.879102842222222

00:49:06.809 --> 00:49:09.446 slow growing nature of the tumor.

NOTE Confidence: 0.879102842222222

00:49:09.450 --> 00:49:11.776 So if you think about it in

NOTE Confidence: 0.879102842222222

00:49:11.776 --> 00:49:14.206 placebo arm of clinical trial,

NOTE Confidence: 0.879102842222222

00:49:14.210 --> 00:49:17.648 you see these tumors takes about

NOTE Confidence: 0.879102842222222

00:49:17.650 --> 00:49:20.723 somewhere between 5 to 18 months median.

NOTE Confidence: 0.879102842222222

00:49:20.723 --> 00:49:24.294 To show about a 20% increase in diameter,

NOTE Confidence: 0.879102842222222

00:49:24.294 --> 00:49:27.925 if you really had a representative Model 1,

NOTE Confidence: 0.879102842222222

00:49:27.925 --> 00:49:29.700 those models are very difficult

NOTE Confidence: 0.879102842222222

00:49:29.700 --> 00:49:30.765 to keep alive.

NOTE Confidence: 0.879102842222222

00:49:30.770 --> 00:49:33.185 Second, will take you years to run

NOTE Confidence: 0.879102842222222

00:49:33.185 --> 00:49:34.969 one single experiment in the lab.

NOTE Confidence: 0.879102842222222

00:49:34.970 --> 00:49:36.218 So it's it's very,

NOTE Confidence: 0.879102842222222

00:49:36.218 --> 00:49:37.444 very, very challenging.

NOTE Confidence: 0.879102842222222

00:49:37.444 --> 00:49:39.729 There are models out there,  
NOTE Confidence: 0.8791028422222222

00:49:39.730 --> 00:49:42.442 but many of them are altering in such  
NOTE Confidence: 0.8791028422222222

00:49:42.442 --> 00:49:44.820 a fundamental way that I don't think  
NOTE Confidence: 0.8791028422222222

00:49:44.820 --> 00:49:47.050 they represent your end of biology.  
NOTE Confidence: 0.8791028422222222

00:49:47.050 --> 00:49:49.990 So if you look at the published  
NOTE Confidence: 0.8791028422222222

00:49:49.990 --> 00:49:51.250 cell lines and.  
NOTE Confidence: 0.8791028422222222

00:49:51.250 --> 00:49:54.687 In in the the models out there,  
NOTE Confidence: 0.8791028422222222

00:49:54.690 --> 00:49:56.850 many of them highlighting yellow,  
NOTE Confidence: 0.8791028422222222

00:49:56.850 --> 00:50:00.126 have mutation that do not occur naturally.  
NOTE Confidence: 0.8791028422222222

00:50:00.130 --> 00:50:04.568 While differentiating Nets with P53 and RB.  
NOTE Confidence: 0.8791028422222222

00:50:04.570 --> 00:50:06.810 The remaining usually are  
NOTE Confidence: 0.8791028422222222

00:50:06.810 --> 00:50:11.290 unknown in terms of P53RB status.  
NOTE Confidence: 0.8791028422222222

00:50:11.290 --> 00:50:12.986 So here's the conundrum.  
NOTE Confidence: 0.8791028422222222

00:50:12.986 --> 00:50:15.530 You need a model that's grows  
NOTE Confidence: 0.8791028422222222

00:50:15.611 --> 00:50:17.886 fast enough to actually take.  
NOTE Confidence: 0.8791028422222222

00:50:17.890 --> 00:50:19.970 And can generate enough material



NOTE Confidence: 0.879102842222222

00:50:19.970 --> 00:50:23.010 that you can actually do experiments,

NOTE Confidence: 0.879102842222222

00:50:23.010 --> 00:50:26.754 but you still need to represent the the

NOTE Confidence: 0.879102842222222

00:50:26.754 --> 00:50:29.890 neuroendocrine slow growing biology.

NOTE Confidence: 0.879102842222222

00:50:29.890 --> 00:50:32.248 So how do we tackle this?

NOTE Confidence: 0.879102842222222

00:50:32.250 --> 00:50:34.518 One of the efforts we've been doing

NOTE Confidence: 0.879102842222222

00:50:34.518 --> 00:50:37.489 in our lab is using a genetically

NOTE Confidence: 0.879102842222222

00:50:37.489 --> 00:50:40.369 engineered patient derived organo way models.

NOTE Confidence: 0.879102842222222

00:50:40.370 --> 00:50:42.128 So what are we doing here?

NOTE Confidence: 0.879102842222222

00:50:42.130 --> 00:50:45.264 We know that if you alter P53 or RV.

NOTE Confidence: 0.879102842222222

00:50:45.264 --> 00:50:47.154 These these things will grow

NOTE Confidence: 0.879102842222222

00:50:47.154 --> 00:50:49.250 and take and proliferate,

NOTE Confidence: 0.879102842222222

00:50:49.250 --> 00:50:52.480 but you don't want the P53RB L you

NOTE Confidence: 0.879102842222222

00:50:52.480 --> 00:50:54.330 know altered when you're testing,

NOTE Confidence: 0.879102842222222

00:50:54.330 --> 00:50:58.686 studying new drugs or understanding the

NOTE Confidence: 0.9402536

00:50:58.690 --> 00:51:01.250 the biology of Nets.

NOTE Confidence: 0.9402536

00:51:01.250 --> 00:51:04.358 So we are using a lenty viral  
NOTE Confidence: 0.9402536

00:51:04.358 --> 00:51:06.776 vector to introduce essentially  
NOTE Confidence: 0.9402536

00:51:06.776 --> 00:51:09.602 doxycycline inducible alterations  
NOTE Confidence: 0.9402536

00:51:09.602 --> 00:51:12.930 in key proliferation pathways.  
NOTE Confidence: 0.9402536

00:51:12.930 --> 00:51:15.700 So the idea is you.  
NOTE Confidence: 0.9402536

00:51:15.700 --> 00:51:18.340 Essentially putting a growth on  
NOTE Confidence: 0.9402536

00:51:18.340 --> 00:51:21.468 and off switch into the patient  
NOTE Confidence: 0.9402536

00:51:21.468 --> 00:51:24.396 tumor samples and then you control  
NOTE Confidence: 0.9402536

00:51:24.396 --> 00:51:27.624 it with in this case doxycycline.  
NOTE Confidence: 0.9402536

00:51:27.624 --> 00:51:31.780 We're using either SV40 large T antigen  
NOTE Confidence: 0.9402536

00:51:31.780 --> 00:51:37.950 behind a the behind the promoter or  
NOTE Confidence: 0.9402536

00:51:37.950 --> 00:51:41.636 a altered P53R273 because the P53.  
NOTE Confidence: 0.9402536

00:51:41.636 --> 00:51:45.111 Acts as a tetramer when even one  
NOTE Confidence: 0.9402536

00:51:45.111 --> 00:51:47.115 copy is is actually mutated.  
NOTE Confidence: 0.9402536

00:51:47.115 --> 00:51:49.290 Is in Paris its function  
NOTE Confidence: 0.942029494117647

00:51:51.450 --> 00:51:53.258 still a lot of work to do to

NOTE Confidence: 0.942029494117647  
00:51:53.258 --> 00:51:54.936 figure this out because there  
NOTE Confidence: 0.942029494117647  
00:51:54.936 --> 00:51:56.488 are many different variations.  
NOTE Confidence: 0.942029494117647  
00:51:56.490 --> 00:51:57.846 You can do this.  
NOTE Confidence: 0.942029494117647  
00:51:57.846 --> 00:52:01.009 You can directly in fact the primary cells,  
NOTE Confidence: 0.942029494117647  
00:52:01.010 --> 00:52:02.570 you can grow them in organizing.  
NOTE Confidence: 0.942029494117647  
00:52:02.570 --> 00:52:06.562 In fact the organize and what's the right  
NOTE Confidence: 0.942029494117647  
00:52:06.562 --> 00:52:09.750 condition and how to solve this work.  
NOTE Confidence: 0.942029494117647  
00:52:09.750 --> 00:52:11.100 We're happy to show that  
NOTE Confidence: 0.942029494117647  
00:52:11.100 --> 00:52:11.910 we're making progress,  
NOTE Confidence: 0.942029494117647  
00:52:11.910 --> 00:52:15.247 that we can actually use the system to  
NOTE Confidence: 0.942029494117647  
00:52:15.247 --> 00:52:20.149 make your endocrine tumor organoids grow  
NOTE Confidence: 0.942029494117647  
00:52:20.150 --> 00:52:22.148 because the previous attempts to organize,  
NOTE Confidence: 0.942029494117647  
00:52:22.150 --> 00:52:23.590 while you can use growth  
NOTE Confidence: 0.942029494117647  
00:52:23.590 --> 00:52:25.030 factor to keep them alive,  
NOTE Confidence: 0.942029494117647  
00:52:25.030 --> 00:52:26.170 they don't really grow.  
NOTE Confidence: 0.942029494117647

00:52:26.170 --> 00:52:28.916 So the only way you can study them is  
NOTE Confidence: 0.942029494117647

00:52:28.916 --> 00:52:31.478 to have a constant stream of material  
NOTE Confidence: 0.942029494117647

00:52:31.478 --> 00:52:33.630 coming from the operating room.  
NOTE Confidence: 0.942029494117647

00:52:33.630 --> 00:52:35.670 But each time is a little bit different,  
NOTE Confidence: 0.942029494117647

00:52:35.670 --> 00:52:39.570 right? So we're hoping that.  
NOTE Confidence: 0.942029494117647

00:52:39.570 --> 00:52:42.426 Over the next month to year to fully  
NOTE Confidence: 0.942029494117647

00:52:42.426 --> 00:52:44.588 characterize all the these organized  
NOTE Confidence: 0.942029494117647

00:52:44.588 --> 00:52:46.752 that we're developing in terms  
NOTE Confidence: 0.942029494117647

00:52:46.752 --> 00:52:49.489 of what what is staying the same,  
NOTE Confidence: 0.942029494117647

00:52:49.490 --> 00:52:52.297 what is being altered and to what  
NOTE Confidence: 0.942029494117647

00:52:52.297 --> 00:52:55.460 extent we can reverse the P53  
NOTE Confidence: 0.942029494117647

00:52:55.460 --> 00:52:59.798 and and and SV40 induce changes,  
NOTE Confidence: 0.942029494117647

00:52:59.798 --> 00:53:03.410 we show all the doxycycline to do  
NOTE Confidence: 0.942029494117647

00:53:03.508 --> 00:53:06.946 drug screening or study the biology.  
NOTE Confidence: 0.942029494117647

00:53:06.950 --> 00:53:09.173 So I'm going to end the talk here and  
NOTE Confidence: 0.942029494117647

00:53:09.173 --> 00:53:11.389 maybe just a few minutes for questions.

NOTE Confidence: 0.942029494117647  
00:53:11.390 --> 00:53:11.470 You  
NOTE Confidence: 0.6325332  
00:53:24.760 --> 00:53:27.320 can say it there. Any questions  
NOTE Confidence: 0.941691228571429  
00:53:27.320 --> 00:53:30.197 from the audience or from or online,  
NOTE Confidence: 0.941691228571429  
00:53:30.200 --> 00:53:32.120 maybe one, see if anyone in the chat,  
NOTE Confidence: 0.893761866666667  
00:53:34.240 --> 00:53:35.680 I'll, I'll ask the first question,  
NOTE Confidence: 0.893761866666667  
00:53:35.680 --> 00:53:38.760 what are you most excited about from a  
NOTE Confidence: 0.893761866666667  
00:53:38.760 --> 00:53:40.799 therapeutic standpoint in the next decade?  
NOTE Confidence: 0.950317  
00:53:41.920 --> 00:53:44.600 That's a tough question.  
NOTE Confidence: 0.950317  
00:53:44.600 --> 00:53:48.146 You know I I I think there's still a role  
NOTE Confidence: 0.950317  
00:53:48.146 --> 00:53:51.988 for immunotherapy but probably not with  
NOTE Confidence: 0.950317  
00:53:51.988 --> 00:53:55.528 existing checkpoint inhibitors but maybe  
NOTE Confidence: 0.950317  
00:53:55.528 --> 00:53:57.812 within except for maybe subpopulations.  
NOTE Confidence: 0.950317  
00:53:57.812 --> 00:54:00.170 That's one of the things we're  
NOTE Confidence: 0.950317  
00:54:00.232 --> 00:54:02.656 learning is although tumor tumor  
NOTE Confidence: 0.950317  
00:54:02.656 --> 00:54:05.596 mutational burden is generally low,  
NOTE Confidence: 0.950317

00:54:05.600 --> 00:54:09.200 you're in the patients live a long time.

NOTE Confidence: 0.950317

00:54:09.200 --> 00:54:11.050 So that tumor mutation burden

NOTE Confidence: 0.950317

00:54:11.050 --> 00:54:12.900 actually may change over time.

NOTE Confidence: 0.950317

00:54:12.900 --> 00:54:15.978 If you look late in the course of disease,

NOTE Confidence: 0.950317

00:54:15.980 --> 00:54:19.396 you may find you know patients will

NOTE Confidence: 0.950317

00:54:19.396 --> 00:54:21.340 benefit from those those sort of

NOTE Confidence: 0.950317

00:54:21.401 --> 00:54:23.049 treatments especially interesting is

NOTE Confidence: 0.950317

00:54:23.049 --> 00:54:25.940 like your work with Timozola mine right,

NOTE Confidence: 0.950317

00:54:25.940 --> 00:54:28.382 because these are Asians that tend

NOTE Confidence: 0.950317

00:54:28.382 --> 00:54:31.375 to induce tumor mutations and and may

NOTE Confidence: 0.950317

00:54:31.375 --> 00:54:33.535 increase tumor orientation will burden.

NOTE Confidence: 0.950317

00:54:33.540 --> 00:54:36.150 So that's actually I think the

NOTE Confidence: 0.950317

00:54:36.150 --> 00:54:37.455 relevant sequencing question.

NOTE Confidence: 0.950317

00:54:37.460 --> 00:54:38.460 When you use that early,

NOTE Confidence: 0.950317

00:54:38.460 --> 00:54:40.372 does that mean later on they have a

NOTE Confidence: 0.950317

00:54:40.372 --> 00:54:42.738 high T MB and you can go back with I/O,

NOTE Confidence: 0.950317  
00:54:42.740 --> 00:54:43.284 that sort of things?  
NOTE Confidence: 0.950317  
00:54:43.284 --> 00:54:43.420 Yeah.  
NOTE Confidence: 0.950317  
00:54:43.420 --> 00:54:43.620 Kevin,  
NOTE Confidence: 0.951994233333333  
00:54:47.340 --> 00:54:48.939 thanks. Doctor Yellen,  
NOTE Confidence: 0.951994233333333  
00:54:48.939 --> 00:54:52.229 can you comment given the expanding  
NOTE Confidence: 0.951994233333333  
00:54:52.229 --> 00:54:54.481 armamentarian and systemic agents  
NOTE Confidence: 0.951994233333333  
00:54:54.481 --> 00:54:57.804 where you see the evolving role  
NOTE Confidence: 0.951994233333333  
00:54:57.804 --> 00:55:00.379 of surgical therapy fitting in?  
NOTE Confidence: 0.951994233333333  
00:55:00.380 --> 00:55:02.920 It's complicated historically?  
NOTE Confidence: 0.951994233333333  
00:55:02.920 --> 00:55:04.970 Depending on where you are  
NOTE Confidence: 0.951994233333333  
00:55:04.970 --> 00:55:06.909 and who you work with,  
NOTE Confidence: 0.951994233333333  
00:55:06.910 --> 00:55:11.327 what the landscape is and we have  
NOTE Confidence: 0.951994233333333  
00:55:11.327 --> 00:55:15.062 felt like surgical cyto reduction  
NOTE Confidence: 0.951994233333333  
00:55:15.062 --> 00:55:18.606 has a role in this disease.  
NOTE Confidence: 0.951994233333333  
00:55:18.606 --> 00:55:21.534 But I I don't know that that's  
NOTE Confidence: 0.951994233333333

00:55:21.534 --> 00:55:23.790 as much the case the current  
NOTE Confidence: 0.9519942333333333

00:55:23.868 --> 00:55:26.228 era or it will be in the future.  
NOTE Confidence: 0.9519942333333333

00:55:26.230 --> 00:55:27.910 I think that's the great question.  
NOTE Confidence: 0.9519942333333333

00:55:27.910 --> 00:55:30.080 I think there's still be a very  
NOTE Confidence: 0.9519942333333333

00:55:30.080 --> 00:55:31.818 important role for cyto reduction  
NOTE Confidence: 0.9519942333333333

00:55:31.818 --> 00:55:33.678 in surgery in this disease.  
NOTE Confidence: 0.9519942333333333

00:55:33.680 --> 00:55:34.560 If nothing,  
NOTE Confidence: 0.9519942333333333

00:55:34.560 --> 00:55:37.176 it actually gives the patient a  
NOTE Confidence: 0.9519942333333333

00:55:37.176 --> 00:55:39.256 potentially a long treatment free  
NOTE Confidence: 0.9519942333333333

00:55:39.256 --> 00:55:41.365 interval from systemic therapy and  
NOTE Confidence: 0.9519942333333333

00:55:41.365 --> 00:55:44.480 although the time course here is long,  
NOTE Confidence: 0.9519942333333333

00:55:44.480 --> 00:55:46.775 so metastatic small bowel patients  
NOTE Confidence: 0.9519942333333333

00:55:46.775 --> 00:55:49.680 are living 8 to 10 years.  
NOTE Confidence: 0.9519942333333333

00:55:49.680 --> 00:55:51.720 But if you ask the patient they will  
NOTE Confidence: 0.9519942333333333

00:55:51.720 --> 00:55:53.875 say 8 to 10 years is not enough,  
NOTE Confidence: 0.9519942333333333

00:55:53.880 --> 00:55:54.191 right?



NOTE Confidence: 0.951994233333333

00:55:54.191 --> 00:55:56.057 So I think there's still room

NOTE Confidence: 0.951994233333333

00:55:56.057 --> 00:55:58.071 to use more modality including

NOTE Confidence: 0.951994233333333

00:55:58.071 --> 00:55:59.589 surgery and international

NOTE Confidence: 0.951994233333333

00:55:59.589 --> 00:56:02.119 radiology technique and so forth.

NOTE Confidence: 0.918433135

00:56:04.610 --> 00:56:08.490 The surgery of symptoms,

NOTE Confidence: 0.918433135

00:56:08.490 --> 00:56:12.410 it certainly can mean, yeah,

NOTE Confidence: 0.918433135

00:56:12.410 --> 00:56:14.165 you know there's many different

NOTE Confidence: 0.918433135

00:56:14.165 --> 00:56:16.697 ways it can in you know some

NOTE Confidence: 0.918433135

00:56:16.697 --> 00:56:18.628 cases patients have essentially

NOTE Confidence: 0.918433135

00:56:18.628 --> 00:56:21.258 abdominal discomfort from a local

NOTE Confidence: 0.918433135

00:56:21.258 --> 00:56:24.120 tumor with nodes and the surgical

NOTE Confidence: 0.918433135

00:56:24.120 --> 00:56:26.781 resection will bypass can be very

NOTE Confidence: 0.918433135

00:56:26.781 --> 00:56:28.836 important for them even though

NOTE Confidence: 0.918433135

00:56:28.836 --> 00:56:31.234 palliative and patients who have.

NOTE Confidence: 0.918433135

00:56:31.234 --> 00:56:33.218 Severe Carson syndrome sometime

NOTE Confidence: 0.918433135

00:56:33.218 --> 00:56:35.014 refractive therapy and benefit  
NOTE Confidence: 0.918433135

00:56:35.014 --> 00:56:36.854 from the bulking all types  
NOTE Confidence: 0.954789557777778

00:56:40.420 --> 00:56:42.085 should there's an increase in  
NOTE Confidence: 0.954789557777778

00:56:42.085 --> 00:56:43.417 incidence but also survival.  
NOTE Confidence: 0.954789557777778

00:56:43.420 --> 00:56:45.730 Are you able to kind of differentiate  
NOTE Confidence: 0.954789557777778

00:56:45.730 --> 00:56:47.368 increased diagnosis of otherwise  
NOTE Confidence: 0.954789557777778

00:56:47.368 --> 00:56:49.548 ability versus advances in therapy  
NOTE Confidence: 0.954789557777778

00:56:49.548 --> 00:56:52.981 or you know parse this out? Yeah.  
NOTE Confidence: 0.954789557777778

00:56:52.981 --> 00:56:55.510 So I think one of the ways we're looking  
NOTE Confidence: 0.954789557777778

00:56:55.578 --> 00:56:58.021 at the survival changes is limiting our  
NOTE Confidence: 0.954789557777778

00:56:58.021 --> 00:57:00.600 analysis to those with metastatic disease.  
NOTE Confidence: 0.954789557777778

00:57:00.600 --> 00:57:03.050 There are still very much some limitations  
NOTE Confidence: 0.954789557777778

00:57:03.050 --> 00:57:05.476 when you look at that sort of data.  
NOTE Confidence: 0.954789557777778

00:57:05.480 --> 00:57:07.811 But I think the large registry is  
NOTE Confidence: 0.954789557777778

00:57:07.811 --> 00:57:09.867 probably still the best way to look  
NOTE Confidence: 0.954789557777778

00:57:09.867 --> 00:57:12.084 at the survival data because when

NOTE Confidence: 0.954789557777778

00:57:12.084 --> 00:57:14.239 you look at individual institutions,

NOTE Confidence: 0.954789557777778

00:57:14.240 --> 00:57:16.354 you have a lot of referral bias.

NOTE Confidence: 0.954789557777778

00:57:16.360 --> 00:57:17.760 You know, those patients who

NOTE Confidence: 0.954789557777778

00:57:17.760 --> 00:57:18.880 has surgery are cured,

NOTE Confidence: 0.954789557777778

00:57:18.880 --> 00:57:20.911 they don't come to tertiary centers, right.

NOTE Confidence: 0.954789557777778

00:57:20.911 --> 00:57:22.866 They're going on and living

NOTE Confidence: 0.954789557777778

00:57:22.866 --> 00:57:24.039 their normal lives.

NOTE Confidence: 0.954789557777778

00:57:24.040 --> 00:57:26.530 And so the large registry still

NOTE Confidence: 0.954789557777778

00:57:26.530 --> 00:57:29.129 have a very important role there.

NOTE Confidence: 0.954789557777778

00:57:29.130 --> 00:57:32.042 And the increase in incidence is happening

NOTE Confidence: 0.954789557777778

00:57:32.042 --> 00:57:35.086 in distinct areas like rectal is you

NOTE Confidence: 0.954789557777778

00:57:35.086 --> 00:57:37.331 know because the screen colonoscopy

NOTE Confidence: 0.954789557777778

00:57:37.331 --> 00:57:41.110 you're finding lot of tiny rectal,

NOTE Confidence: 0.954789557777778

00:57:41.110 --> 00:57:43.630 you're in the consumers which also

NOTE Confidence: 0.954789557777778

00:57:43.630 --> 00:57:46.528 is linked to specific race and

NOTE Confidence: 0.954789557777778

00:57:46.528 --> 00:57:49.055 ethnicity issues and in in in small

NOTE Confidence: 0.954789557777778

00:57:49.055 --> 00:57:50.540 pancreatic urine the consumer is

NOTE Confidence: 0.954789557777778

00:57:50.598 --> 00:57:52.308 going to be something we're going

NOTE Confidence: 0.954789557777778

00:57:52.308 --> 00:57:54.491 to have to deal with just the

NOTE Confidence: 0.954789557777778

00:57:54.491 --> 00:57:56.126 increase CT start getting done.

NOTE Confidence: 0.896334164

00:57:59.210 --> 00:58:00.310 Well, thank you so much

NOTE Confidence: 0.896334164

00:58:00.310 --> 00:58:01.410 Doctor Yao for coming today.