Good afternoon, everybody. I think we’ll go ahead and get started. So greetings to everybody in the room and to everyone online. And welcome to Yale Cancer Center, Grand Rounds. My name is Pam Koons. I’m the director of the Center for GI Cancers, and it is a great honor to introduce my friend Doctor James Yao as the Norbert Schnog Endowed Lecturer. So Doctor Yao is a Professor and
Chair in the Department of GI Medical Oncology at the University of MD Anderson Cancer Center, and he received his medical degree from Baylor College of Medicine and completed his fellowship at MD Anderson. So for the last two decades, Dr. Yao and colleagues have really transformed the field of neuroendocrine tumors. So that is how I know him and he has led practice changing randomized clinical trials, specifically the family of radiant clinical trials that include the drug everolimus that led to FD approvals for pancreatic net, lung net and GI and undercon tumors.
I was also a strong advocate of mentoring and education. He is a founding member and past chairman of the North American Neuroendocrine Tumor Society of which I am the president of this year. And then through that society can helped establish two young investigator awards that fund early career investigators. He’s also the past chair of the NCIA and under consumer task force. And during his tenure, led more than 50% of the multicentered clinical trials developed through...
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
remains and for you know what we need to.

Make the next century even better than the what we’ve done so far and it’s a plug for nanettes this this rainbow at this photograph was from one of the nanettes meetings which we held at the Grand T ea Towns National Park and let’s see here’s my disclosures.

So the field of neuroendocrine tumor started with open door for first described this entity about in 1907 he described this group disease is cancer described this group disease is cancer like or part of what tumors are more slow growing than the typical carcinomas.
The 1st century of net has been a century where we’ve learned a lot about the Natural History of the disease. Understand a lot of the endocrine manifestations of neuroendocrine tumors and we also learn a lot about epidemiology of disease in semester biology. However, the number of therapeutic introduced over this period is actually relatively sparse prior to I would say the more recent approvals. There was only one drug that was FDA approved for oncologic control and that streptosis dosen for pancreatic net. There were two drugs approved for hormonal control of the neuroendocrine tumors.
This is certainly not for lack of effort. This is a classic lecture by Chuck Mortell where he talks about his odyssey in the land of small tumors as you can see on the table on the right. There's been numerous agents that were studied but these chemotherapy agents did not really have that much activity with the exception of DTIC and streptozosin in pancreatic neuroendocrine tumors. Another thing you'll see is that because you know this disease was thought to be rare and he that's why he used the term land.
of small tumors.

The studies were actually very small and I think that really limited the progress. These were all single arm studies and some of them only containing less than a handful of patients. So one of the first things I think we needed to understand about neuroendocrine tumors is that the disease is probably actually more common than we think. One of the analysis we did in from the SEAR database and we showed that comparing to other malignant neoplasms diagnose incidence of neuroendocrine tumor is continually rising and since this we have a kind of updated the data.
and in you know when when it was in 2004
the incident was about 5 per 100,000,
2012 about the.
Recent data would happen publish
it is well above 8 per 100,000.
Another thing that's different about
this disease is because the disease
is more slower growing patient live
a lot a lot longer with the cancer.
So essentially the prevalence
statistic which is the number of
patients who are potentially in
need of care because there are life
with disease is actually higher.
So if you did limited duration prevalence analysis which we did from the SEAR data it the US prevalence last we looked was above 170,000. So certainly this is still at least for the moment below the 200,000 cut off which the FDA uses this definition of rare disease and certainly if you further divide you’re in the consumer subtypes that will remain. Rare for quite a quite a long time. So one of the question to think about is, was this rising incidence and so forth is what’s going on here. There are environmental factors that are increasing the incidence of
neuroendocrine tumor or perhaps this is just better recognition of the disease. Certainly we are seeing more neuroendocrine tumors in some case related in the gastric urine the consumer. Related to use of PPI's, but I think for the most part these neuroendocrine tumor has always been there. So here are a couple of classic studies in two in, studies in two in, in Carcino tumors are really talking about intestinal neuroendocrine tumors are two studies that included 15,000 autopsies and these tumors
are found in about 1% of autopsies.

So these are patients who died from unrelated causes.

And most mostly lift out their natural lifespan without having them diagnosed.

So really the question is not so much whether they’re increasing in

much whether they’re increasing in and what are environmental factors,

but what transforms some of these small tumors into malignant ones but

pancreatic neurin different tumors.

There’s one study that was in Hong Kong,

again 11,000 autopsy one in 1000.

Autopsy specimen had a pancreatic urine.

The consumer,

if you look for them compare this
00:07:56.944 --> 00:07:59.206 to a diagnosed instance more like
00:07:59.206 --> 00:08:02.255 in the range of maybe three to five
00:08:02.255 --> 00:08:03.747 per million per year.
00:08:03.750 --> 00:08:06.630 That tells you probably less than
00:08:06.630 --> 00:08:09.030 1% of pancrea and urine.
00:08:09.030 --> 00:08:11.995 The consumers that are present
00:08:11.995 --> 00:08:15.094 and in patients eventually become
00:08:15.094 --> 00:08:16.346 clinically relevant.
00:08:16.350 --> 00:08:18.252 This is posing a challenge for
00:08:18.252 --> 00:08:20.170 us as we move forward.
00:08:20.170 --> 00:08:23.000 Because the increased use of
00:08:23.000 --> 00:08:24.882 imaging nowadays you can hardly
00:08:24.882 --> 00:08:26.850 go to the ER with abdominal
00:08:26.920 --> 00:08:29.683 pain without leaving the ER with a CT scan.
00:08:29.690 --> 00:08:33.450 So we’re finding a lot of small tiny
pancreatic neuroendocrine tumors,

some of them in the head of pancreas

where if you try to operate on them may,

may be a quite a morbid

and higher risk procedure.

So understanding which of these can be

left alone and patients are going to.

Essentially lived with disease

in their natural lifespan,

which one is near to near that

really needs to intervene on is

going to be important going forward.

So the other thing that the with you know

this information about the incidence

and prevalence in your endocrine tumors

is that the patient advocacy groups,
you know in the past decades has really got engaged.
There are the stories of patients who have had. Long history of symptom maybe that went undiagnosed for decades. So there’s a strive to see whether we can recognize the symptoms earlier and diagnose the cancer earlier. But the challenge is the symptoms that are associated with these tumors are fairly vague and common in the general population. So this is study we did from CR Medicare database. Essentially, looked at the year prior.
to their neuron cancer diagnosis, what kind of doctor do they go visit and what sort of symptoms do they complain of? You can see, well, statistically significant for most of these. There are differences in rates of hypertension, abdominal pain, heart failure, diarrhea, and peripheral edema. But if you try to look at a positive predictive value of these symptoms when you’re in the current tumor. They’re all very, very low because they’re very common in the general population. The newer endocrine field also is
a field where the very terminology we or she used to describe the disease has been evolving in the over the past decades. In the older time frame, the worst like carcinoy eyelid spells were commonly used. And it’s moved to newer endocrine neoplasms and there’s grading initially just grade 1-2 and now differentiation is added to add a historical context on why the the constant change almost feels like in terminology is that this field you know at the time when these
I think people didn’t really know where the right cutoff is in terms of the disease. It’s more based on consensus and recurrence and relate the true biology. What beginning to understand is clearly there’s two different groups well differentiated, you’re in the consumer grade 1-2 and three and they’re mostly grade 1-2 and the poorly differentiated urine carcinomas. Which is a completely different disease that has nothing to do with the other.
And there are also differences in terms of the primary site. We'll talk a little bit about the molecular landscape and genomics of the different primary sites, but they are characterized by relatively low tumor mutational burden, but these tumors actually have high rates of chromosomal instability. You see instead of point mutations, a large scale chromosomal changes. The most common mutation seen is M and the same with pancreas M EM1. But here you also see DAX and ATRX and...
intestinal relatively few somatic mutations, but you see frequent loss of chromosome 18, the poorly differential neuro endocrine tumor. It's probably really a mixed bag a lot of time these are essentially transformed versions of adenocarcinoma, occasionally transformed lower grade tumor after certain types of therapy, but they're characterized by a very fast growth rate and mutation in TP53 and RV are the most common mutations. So if you understand the genomics of neuroendocrine tumors, so one of the things we did is leverage our large phase three clinical trials.
We did a series of trials called radium trials looking at everolimus where over about 1000 patients across you. Four studies were enrolled and where we can get the tumor. We did a whole genome analysis. We saw relatively few somatic mutations, but what is striking is the amount of largescale chromosomal changes that you see chromosomal gain and chromosomal loss and these actually have very significant prognostic value. For example in pancreatic neuron different tumors, patient with high chromosomal instability.
actually have a much better prognosis in the advanced disease setting. And we'll talk about a little bit in the next few slides why that is because it is a specific carcinogenesis pathway that's implying here. And then we see also those patients with intestinal neuroendocrine tumor with loss of chromosome 18 also have a far better prognosis than those who do not have a loss of chromosome 18 whereas the loss of chromosome 3. On the lung neuron, different tumors pertains to a poor prognosis. So one of the things that really always
short struck me is really what’s going on with pancreatic neural in the consumer. It’s really one of my favorite diseases in the sense there’s so much, so much stuff here. So you see here when we sequence the pancreatic neural in the tumors. They roughly fall into three categories when you look at the host whole genome in terms of chromosomal changes. In the first group here, Group One, they lose one copy of 11 of the 22 chromosomes. In the second group, there’s loss of 1 copy of the 11 chromosomes,
one copy of 11 chromosomes. And gain on the complementary 11 chromosomes and then there’s a group that are relatively stable in terms of chromosomal abnormalities. And on the bottom panel is little small. So I’ll just talk through it a little bit and it’s important in the sense that you can actually link these chromosomal changes to specific mutations that are present in if you look at this. The chromosomal instability tumors so that’s these are in Gray and in red are essentially are in rich for patients with M EM1 mutations.
So what's the link between M EM1 mutation and and this and the M EM1 mutations is also linked with DAX whereas the ATRX mutations. Essentially also involved in a TRX and DAX are involved in alternative links. Near telomeres can be associated with chromosome instability in absence of M EM1. So the ATRX by itself the mutation seems to drive this phenomenon. So what we see here is then you see DAX and ATRX mutations associated chromosomal instability. And you have, you know loss of 1 copy of 11 chromosome.
and gain on the complementary 11 chromosomes and the strong association between men one mutation and DAX in the combination of men one DAX mutation with chromosome instability. So what’s going on here? Why are we losing one copy of 11 chromosome and gaining on the complementary 11 chromosomes? For whatever reason, you’re essentially what’s actually going on is you’re losing one copy of 11 chromosomes and this in some patients, probably due to happily insufficiency, is leading to whole genome duplication. So essentially these are copy neutral LOH.
They are occurring essentially in the game because the whole genome duplication. Is occurring in the complementary 11 chromosomes. So what’s the story here? While the most common mutation in your endocrine tumor is man one specifically endocrine tumor is man one specifically linked to pancreatic neuroendocrine tumors occurring roughly about 40% of patients and also associated with lung neuroendocrine tumors. What do we know about man one biology? It is certainly is epigenetic regulators involved in modulating P27 and it’s actually involved.
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 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
Trial and Nurses Health Study that involved about 3600 patients, the group this group evaluated 743 snips and try to correlate that with essentially peripheral blood telomere lens. The only gene that fell out to be important was actually men and. It was the most important implicated in control of telomere lens for in the study. So the story of telomeres, you know as you know the telomeres are in the caps and end of our chromosomes and Menon is driving cell cycle in here. The telomere lens is going to get
short as telomere lens gets short.

Essentially usually the cancer cell dies where you need to turn on some way of maintenance of telomere or Linston telomeres.

For most cancers this is essentially activation of telomeres, but in a few cancers and in pancreatic neuroendocrine tumors, the mechanism that’s gets activated as alternative linsing of telomeres.

How do we know this? This is some slice courtesy of Christopher Heefy where he showed essentially in neuro endocrine tumor that has well typed Dax ATRX you see
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

NOTE Confidence: 0.933544666666667

00:21:22.357 --> 00:21:24.526 pancreatic neuroendocrine tumor.
NOTE Confidence: 0.933544666666667
The situation is actually reversed in the earlier disease. Essentially what’s going on is that advanced disease the DAX ATRX mutation. Is marking a group of pancrea urine the consumer who goes down a very specific carcinogenic pathway, whereas in the earlier disease this actually the IT pretends to be a worst prognosis. So this is a great study that was done in men, one families. So these are patients with familial mutations in M EM1. What they’re able to show is that.
When the tumors are small, you usually don’t see DAX ETRX mutations and the DAX ETRX mutations occur in tumors that are larger in this case and I think they use a cutoff about 3 centimeters and also happens in patients who have lymph node metastasis. So likely what’s going on is these tumors driven by men one to proliferate these benign tumors. The tilar mirrors are getting shorter and the ones who are able to turn on tilar mirror maintenance throughout.
are the ones that gets larger and

then lead to regional metastasis.

So again, this is just showing

In a recurrence-free survival graph,

those who are turning on health

in the localized setting where

they have three section have

a little bit poor prognosis.

Next I’m going to shift gear a little bit and talk about essentially on the clinical side the development of new novel therapies for neuroendocrine tumors.

So essentially prior to 2007, we only had Streptozosin for your contumor of the pancreas.
00:23:40.000 --> 00:23:42.340 And since then you really have

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

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

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

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

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

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

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

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

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

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

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

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

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

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

NOTE Confidence: 0.93773775

NOTE Confidence: 0.93773775

NOTE Confidence: 0.93773775

NOTE Confidence: 0.93773775

NOTE Confidence: 0.93773775

NOTE Confidence: 0.93773775
right endpoint or in, but the phase three trials are recommended. Overall survival trials, neuroendocrine tumors, we came that out in doing the meeting and realized they will require a probably about two to 3000 patients and probably 8 to 10 years to execute. So that’s why you will see in the subsequent slide most of the approved agents are able to then demonstrate PFS benefit. But we don’t have quite a large sample size needed that demonstrates survival benefit
going going into the systemic randomized space free trials are you know we’re going to talk to them a little bit about different targets. So the first targets we’ll talk about is the Smestan receptor. For a long time prior to this Smestan receptor targeting was Octreotype. For a long time prior to this Smestan receptor targeting was Octreotype. Was approved for control of Carson syndrome it relief flushing and diarrhea in probably about 70% of the patients. But there are a lot of back and forth debate as to whether actually or not is slow cancer grows and it was almost like a little religion.
people either believe it or we they didn’t but what was important is you just need to actually do the trial it turns out and in this phase three trial that’s done by the.

A multicenter German trial in patients were relatively newly diagnosed with small bowel neuroendocrine tumor. They were able to demonstrate improvement progression free survival. A similar trial was conducted as a larger trial and included a broader group of patients including pancreatic and rectal neuroendocrine tumors. And again showing significant benefit.
in terms of progression free survival.

Notice however the hazard ratio for the octerotized study was a little bit lower than the hazard ratio for the land real time study. This is probably a byproduct in terms of the way the trial were executed. It turns out the octerotized study was permanent terminated early. At interim analysis and in there's been subsequent publications and analysing analysis of popular population of studies that can demonstrate while when you terminate a study early for outstanding efficacy,
you tend to overestimate the magnitude of the treatment effect.

And that’s just a byproduct of our early termination because when you terminate a study early, you preserve your ability to test the hypothesis, but not the ability to estimate the magnitude of treatment benefit.

Another way to term to target some mass and receptor is PRR T, which really has become very well, widely used at this point. Again, in the earlier development of PRRT it was not.

It was a lot of a single single
institution studies and you have

these publications in high impact

journals where they purportedly report

a phase two study of 1000 patients.

And you know,

but actually what was needed for

really demonstrating benefit and

approval is a randomized phase three

trial which you can do actually was

far fewer than thousand patients.

So this takes advantage of the

fact that semastin receptors are

present on your endocrine cancer

cells in 7080% of the cases.

Specifically for semastin receptor

Specifically for semastin receptor
When the lichen binds to the receptor, it is internalized. So these agents essentially take Lutetian 177 and lead to very good efficacy. There's also a role for targeted therapy in neuroendocrine tumors. One of the drugs that we were involved in developing is everolimus of affinitor targeting the emptor pathway. The Radian 3 trial was the first to report out and for pancreatic neuroendocrine tumors and here you saw benefiting progression free survival from median 4.6 months to 11 months.
And hazard ratio was .35 here in overall survival because the crossover we did our PFST analysis rank preserving structure failure time showing like there's a likely benefit in overall survival, but in because of the crossover these such studies and not these studies are really designed to evaluate overall survival. For Radian 4, this is the phase three study we did in lung and GI neuroendocrine tumors. Again patient were randomized to receive everolimus or placebo.
The PFS improved from 3.9 months to 11 months with a hazard ratio of 0.48 and a trend to our overall survival benefit.

Another targeted agent that’s shown benefit is sunitinib. So Sunita was initially evaluated in a phase two study being that had two cohorts for intestinal neuroendocrine tumors and pancreatic neuroendocrine tumors. All the responses were seen in the pancreatic neuroendocrine group. So it was taken into a phase three trial. The study actually terminated early at an unplanned interim analysis. Nonetheless there it was significant.
benefit demonstrating PFS and then that led to the FDA approval of the drug for pancreatic neuroendocrine tumors. We do believe VEGF inhibitors may have a role in extra pancreatic neuroendocrine tumor as well. This is another phase three trial that I did early in my career, the SWAG O 518. And the in this study patients were randomized from octreotide plus interferon versus octreotide plus Bebasus MAP. Where we’re able to show in this study is that although the response rate improved with Bebasusan MAP and
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 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 --> 00:31:44.659 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
00:31:42.642 --> 00:31:44.659 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
arm is not very carefully what is not well defined.

So there has been others who evaluated veget inhibitors in your in the Contuber. This is a study conducted also in the cooperative group. The Pi is Emily Burksland and patient were randomly assigned to either pizopanit versus placebo. And there there was the benefit in terms of progression free survival also demonstrated in extra pancreatic neuroendocrine tumors. So potentially showing the importance of role of VEGF inhibitor outside
beyond the pancreatic group in terms of phase three studies for extra pancreatic neuroendocrine tumor. And there’s also a study that was performed in two studies that were performing in China with Serofatin NIP, another VEGF or multi kinase inhibitor demonstrating similar magnitude of benefit for Serofatin Nip both in pancreatic net and extra pancreatic net unfortunately the FDA. It’s going to probably require the company to redo the trial because it did not contain it was a purely Chinese population and the population may not fully represent.
the lines of prior therapy Western populations would have been exposed to.

Next I’m going to mention while Doctor Kunz’s trial Ecog 2211, which is actually a very important trial.

Partially because the initial development of Timosolomite were essentially skipped the single agent step they were, you know most of the trials that were published were doublets. So always been a question to feel that whether you need doublets or you know where the agent is, Timosolomite by itself is a sufficient.
00:34:09.434 --> 00:34:11.790 look at this class of agents in pancreatic neuro in the consumers.
NOTE Confidence: 0.948080688888889
00:34:11.790 --> 00:34:13.270 If you dig back into Chuck Mattel's papers and so forth,
NOTE Confidence: 0.948080688888889
00:34:13.270 --> 00:34:16.228 DTIC is active in the disease.
NOTE Confidence: 0.948080688888889
00:34:16.228 --> 00:34:18.910 So this is a trial that compared Timosolomite to Tim Cape at the intern analysis.
NOTE Confidence: 0.948080688888889
00:34:18.910 --> 00:34:21.466 The study met its primary endpoint and showed improvement in progression free survival.
NOTE Confidence: 0.948080688888889
00:34:21.470 --> 00:34:24.534 For our patients with Tim Kay and I think another actually very important finding from this study is the prognostic and significance with association of the MGMT expression in this is a
DNA repair pathway when that often
are methylated MGMT and leading
to low expression and you can see.
That for patients with low MGMT,
the response rate is much higher than
those who have intact MGMT expression.
So if you look at the current treatment
landscape for neuroendocrine tumor,
we have come a long way.
You know in the beginning historically we
only have one agent for pancreatic net.
Now you have number of phase three
clinical trial covering many of the
different in your endocrine tumors.
Essentially these are clustered
around agents that targets these.

These are stable or early disease like

TRILTY and then Realty in the pro

Med and the CLARINET study and in the

studies who tend to target patients

was faster progressing disease PRT

somewhere in the middle that required

progression in the past three years.

And most of the targeted agents

require progression in the past one

year when in the case of Radian 4

progression within the past six months.

So what are some of the remaining

challenges and questions that we

have when you’re in the current

tumor at this point,
one of the question I get asked the most is sequencing, what’s the optimal sequencing of therapy for neuro in the current tumors? So it’s kind of interesting because you’re in the consumers, you had approval a lot of agents while in a short period span of time. So they were not really developing a way where they were specific align first line, second line, third line. Most the drugs were either approved for progressive disease or they were just approved for advanced disease but optimal sequencing.
It’s really talking about which sequence leads to the best overall longterm survival. This is actually extremely difficult question to answer. It’s not about which agent when used first has the longest initial PFS, because if that agent, you know, essentially takes out your kidney or makes it difficult for you receive other agents. And it may not be the best agent to use initially. So almost certainly this is if you really want to answer this question, it needs overall survival endpoint. Well,
here’s the challenge right when for different indications you have different number of treatments available, the approved therapy for lung, there’s only ever limus in peanut you have six agents that are available, approved you can use. A 7th agents demonstrated activity that’s probably works well. You can imagine trying to compare optimal sequences. There’s 5040 sequences, 5040 arms for overall survival. This is not where we want to spend our energy and because I think
likely before evening to solve a simpler question before you actually. To answer the question and complete a trial, the treatment landscape would have changed in the trial design. will probably no longer be valid. And to give an actual example of an attempt to do this, our European colleague contacted the secretor trial. The secretor trial looked to compare the sequence of Ever Linus followed by Streptozosin based chemotherapy or Streptozosin based chemotherapy followed by Ever Linus. They weren’t going to be quite ambitious.
00:38:55.800 --> 00:38:58.480 to try OS as the primary endpoint.

00:38:58.480 --> 00:39:00.960 They were going to look at P FS2.

00:39:00.960 --> 00:39:04.824 So initially are due to a cruel

00:39:04.824 --> 00:39:08.008 issues that they had to do scale

00:39:08.008 --> 00:39:10.216 back their ambitions to look at

00:39:10.216 --> 00:39:13.080 P FS1 as the primary endpoint.

00:39:16.000 --> 00:39:18.775 Yeah, actually showed that although

00:39:18.775 --> 00:39:21.550 Streptozosin set of toxic chemotherapy.

00:39:21.550 --> 00:39:23.790 Was a little bit more toxic but higher,

00:39:23.790 --> 00:39:25.710 had a higher response rate,

00:39:25.710 --> 00:39:28.650 but there was no difference in progression

00:39:28.650 --> 00:39:30.829 free survival between the two arms.

00:39:30.830 --> 00:39:34.400 So higher higher response rate may not

00:39:34.400 --> 00:39:38.150 necessarily lead to a better outcome.
The second most frequent question I get asked about nearing the consumer these days is precision medicines and biomarkers. If you did a search on your end, the consumer and biomarkers on PubMed, you’ll get thousands, probably near 10,000 results back. So what do we know about biomarkers for neuroendocrine tumors? I usually think about biomarkers as two classes. These are prognostic identifying those people who have a better outcome and predictive meaning to actually sorting out individual who are more likely.
But then similar individual without a biomarker to experience a favorable benefit from an exposure to a medical product we environment agents. So the bottom line is who should get this treatment is really the important question for predictive biomarker. Another way to think about the importance of predictive biomarker is really thinking about like who’s going to benefit from treatment if you have a treatment where everybody benefits. Predictive biomarker can almost becomes essentially a prognostic biomarker. It’s probably of less clinical
importance in the situation where half the patient will benefit. A predictive biomarker is super useful and it’s even more important when a smaller group of patients have profound benefit, but most people don’t. So what is actually the situation you are in different tumor which of these waterfall plots do we look like? Fortunately it looks like this whereas a most the patients benefiting from the treatment within their treatment indications. So the challenge of predictive biomarker is essentially you have to randomize more patients all patients. Including patients who don’t have
the biomarker because without that
randomization is very difficult to understand which biomarker is important.
You should do this when the marker is suspected to be predictive but not
proven and you have reliable assay methodology and cut points and there’s reason to expect benefit potentially in biomarker negative patients.

Much more common we seeing oncology these days is this approach which is establishing efficacy of biomarker population which means we only essentially randomize the biomarker positive population. So here you can prove the biomarker positive
benefit patients benefit from new treatment.

But it’s best used when no benefit is expected in bowel marker negative population.

You don’t have any information gained about the bowel marker negative population.

But often sometimes we get it wrong, right. We don’t initially fully understand this.

The classic example in colon cancer is cetuximab. The initial FDA approval in clinical trial was for patients.

Who had e.g. Fr expression on I HC?

Turns out that has nothing to do with whether someone benefits from situximab or not in colorectal cancer.

And the net example is really kind
something I kind of lived through.

After we started a phase three trial, a publication came out in science showing about 15% of the patients with pancreatic net at M Tor pathway mutations.

So I will. I would gladly admit I was a very lucky not to know that when I started the trial. But because it turns out you know extra pancreatic net, none of the patients have mtor pathway mutations, quote mtor pathway mutations, but they all benefited from the therapy and even in the pancreatic net group.
those who had mtor pathway mutations. And didn’t have M Tor pathway mutation have similar magnitude of benefit. That’s not to say that it’s not correct that you know what was published is just means that I don’t think we may sometimes know the full M Tor pathway or how these drugs actually work. Those are biomarkers. In neuroendocrine trials, the question often is asked about the semester and syntactroph in for semester. And like octreotide and Realty, the prominence study actually 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
In early studies and single arm study it looked like those patient who had an early drop in pomegranate had a benefit for patients treated was everolimus. But this turned out actually not to be that useful when we took it to phase three because the placebo patient also had a better outcome as well. So likely this is pointing out some issues with the assay performance and whether we're not you actually have to test these patient multiple times before you get a reliable results.

Another BOW marker attempting to look at the predictive bow marker in terms of...
response is looking at profusion CT in patients treated with veg inhibitors. We're able to show that in patients treated with Bebasusan app is open in a flipper set that essentially baseline parameter and change after treatment correlated with the degree of tumor shrinkage. I think what we learned here is that these are very difficult to do. And very operator dependent. So it's was possible to do it in clinical trial taking it out to the wider clinical practice is challenging. So if you look at a biomarker landscape for neuroendocrine tumor,
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: 0.8791028
00:47:17.910 --> 00:47:19.656 PR T&MGMT for Timosolemai,
NOTE Confidence: 0.8791028
00:47:19.656 --> 00:47:23.148 However, we're still need a lot,
NOTE Confidence: 0.8791028
00:47:23.150 --> 00:47:25.606 lot more work to do in terms of
NOTE Confidence: 0.8791028
00:47:25.606 --> 00:47:29.880 getting real predictive biomarkers.
NOTE Confidence: 0.8791028
00:47:29.880 --> 00:47:31.668 So I mentioned earlier that we
NOTE Confidence: 0.8791028
00:47:31.668 --> 00:47:33.716 have a lot of approved therapy
NOTE Confidence: 0.8791028
00:47:33.716 --> 00:47:36.467 but most of these trial were not
NOTE Confidence: 0.8791028
00:47:36.467 --> 00:47:38.760 designed to ask a survival question.
NOTE Confidence: 0.8791028
00:47:38.760 --> 00:47:42.000 So you know has all this work been
NOTE Confidence: 0.8791028
00:47:42.000 --> 00:47:44.798 approval our patients doing better,
we can look back into the SEAR database again and showing
that the trend in improving,
improving overall survival in patients with great one to two metastatic neuroendocrine tumors.
Suggesting that what we did actually does actually make a real impact.
So next what do you think we need to do to continue the progress in your endocrine tumors?
I think clearly we one thing we learned is the use of robust randomized clinical trials and we shouldn’t be shy about using placebo.
control trial in the right setting.

We do need better availability of neuro in the model for translational research.

I think we have a baseline group of therapy that works now to find the next pathway to target the next target.

I think the neuron models in the lab will really benefit us and we need to obviously explore novel therapeutic approaches.

I’ll just have two more slides.

There’s a real challenge with differentiating your endocrine tumors.

There’s been many attempts to generate
cell lines, xenographs and organize. Principally they are limited by a slow growing nature of the tumor. So if you think about it in placebo arm of clinical trial, you see these tumors takes about somewhere between 5 to 18 months median. To show about a 20% increase in diameter, if you really had a representative Model 1, those models are very difficult to keep alive. Second, will take you years to run one single experiment in the lab. So it’s very, very challenging.
There are models out there, but many of them are altering in such a fundamental way that I don’t think they represent your end of biology. So if you look at the published cell lines and, many of them highlighting yellow, mutation that do not occur naturally. In the the models out there, In in the the models out there, many of them highlighting yellow, mutation that do not occur naturally. While differentiating Nets with P53 and RB. The remaining usually are unknown in terms of P53RB status. So here’s the conundrum. You need a model that’s grows fast enough to actually take and can generate enough material.
that you can actually do experiments, but you still need to represent the the neuroendocrine slow growing biology. So how do we tackle this? One of the efforts we’ve been doing in our lab is using a genetically engineered patient derived organo way models. We know that if you alter P53 or RV. These these things will grow and take and proliferate, but you don’t want the P53RB L you know altered when you’re testing, studying new drugs or understanding the biology of Nets.
So we are using a lentiviral viral vector to introduce essentially doxycycline inducible alterations in key proliferation pathways. So the idea is you essentially putting a growth on and off switch into the patient tumor samples and then you control it with in this case doxycycline. We're using either SV40 large T antigen behind a the behind the promoter or a altered P53R273 because the P53. Acts as a tetramer when even one copy is is actually mutated. Is in Paris its function still a lot of work to do to
00:51:53.258 --> 00:51:54.936 figure this out because there are many different variations.

00:51:56.490 --> 00:51:57.846 You can do this.

00:51:57.846 --> 00:52:01.009 You can directly in fact the primary cells, you can grow them in organizing.

00:52:01.010 --> 00:52:02.570 In fact the organize and what’s the right condition and how to solve this work.

00:52:02.570 --> 00:52:06.562 We’re happy to show that we’re making progress, that we can actually use the system to make your endocrine tumor organoids grow because the previous attempts to organize, while you can use growth factor to keep them alive, they don’t really grow.
So the only way you can study them is to have a constant stream of material coming from the operating room. But each time is a little bit different, right? So we’re hoping that over the next month to year to fully characterize all the organized that we’re developing in terms of what is staying the same, what is being altered and to what extent we can reverse the P53 and SV40 induce changes, we show all the doxycycline to do drug screening or study the biology. So I’m going to end the talk here and maybe just a few minutes for questions.
You can say it there. Any questions from the audience or from online, maybe one, see if anyone in the chat, I'll ask the first question, what are you most excited about from a therapeutic standpoint in the next decade? That's a tough question. You know I think there's still a role for immunotherapy but probably not with existing checkpoint inhibitors but maybe within except for maybe subpopulations. That's one of the things we're learning is although tumor mutational burden is generally low,
you’re in the patients live a long time.

So that tumor mutation burden actually may change over time.

If you look late in the course of disease, you may find you know patients will benefit from those those sort of treatments especially interesting is like your work with Timozola mine right, because these are Asians that tend to induce tumor mutations and and may increase tumor orientation will burden.

So that’s actually I think the relevant sequencing question.

When you use that early, does that mean later on they have a high T MB and you can go back with I/O,
00:54:42.740 --> 00:54:43.284 that sort of things?

00:54:43.284 --> 00:54:43.420 Yeah.

00:54:43.420 --> 00:54:43.620 Kevin,

00:54:47.340 --> 00:54:48.939 thanks. Doctor Yellen,

00:54:48.939 --> 00:54:52.229 can you comment given the expanding

00:54:52.229 --> 00:54:54.481 armamentarian and systemic agents

00:54:54.481 --> 00:54:57.804 where you see the evolving role

00:54:57.804 --> 00:55:00.379 of surgical therapy fitting in?

00:55:00.380 --> 00:55:04.970 Depending on where you are

00:55:04.970 --> 00:55:11.327 what the landscape is and we have

00:55:15.062 --> 00:55:18.606 has a role in this disease.

00:55:18.606 --> 00:55:21.534 But I I don’t know that that’s

00:55:21.534 --> 00:55:24.000 armamentarian and systemic agents
as much the case the current era or it will be in the future. I think that's the great question. I think there's still be a very important role for cyto reduction in surgery in this disease. If nothing, it actually gives the patient a potentially a long treatment free interval from systemic therapy and although the time course here is long, so metastatic small bowel patients are living 8 to 10 years. But if you ask the patient they will say 8 to 10 years is not enough, right?
So I think there's still room to use more modality including surgery and international radiology technique and so forth. The surgery of symptoms, it certainly can mean, yeah, you know there's many different ways it can in you know some cases patients have essentially abdominal discomfort from a local tumor with nodes and the surgical resection will bypass can be very important for them even though palliative and patients who have. Severe Carson syndrome sometime
refractive therapy and benefit
from the bulking all types
should there’s an increase in incidence but also survival.
Are you able to kind of differentiate increased diagnosis of otherwise ability versus advances in therapy or you know parse this out? Yeah.
So I think one of the ways we’re looking at the survival changes is limiting our analysis to those with metastatic disease. There are still very much some limitations when you look at that sort of data. But I think the large registry is probably still the best way to look at the survival data because when
you look at individual institutions, you have a lot of referral bias. You know, those patients who has surgery are cured, they don't come to tertiary centers, right. They're going on and living their normal lives. And so the large registry still have a very important role there. And the increase in incidence is happening in distinct areas like rectal you're finding lot of tiny rectal, you're in the consumers which also is linked to specific race and.
ethnicity issues and issues in small
NOTE Confidence: 0.954789557777778
pancreatic urine the consumer is
NOTE Confidence: 0.954789557777778
something we're going
NOTE Confidence: 0.954789557777778
to have to deal with just the
NOTE Confidence: 0.954789557777778
increase CT start getting done.
NOTE Confidence: 0.896334164
Well, thank you so much
NOTE Confidence: 0.896334164
Doctor Yao for coming today.