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, for those of you who do not know me.

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...
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,
I was also a strong advocate of mentoring and education. He is a founding member and past chairman of the North American Neuroendocrinic Tumour Society of which I am the president of this year. And then through that society can help establish two young investigator awards that fund early career investigators. He’s also the past chair of the NCIA and under consumer task force. 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 the Grand Tea 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 like or part of what tumors are more slow growing than the typical carcinomas.
The 1st century of net has been a 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.
00:04:29.628 --> 00:04:30.789 of small tumors.
NOTE Confidence: 0.957026033333333
00:04:30.790 --> 00:04:34.590 The studies were actually very small and I
NOTE Confidence: 0.957026033333333
00:04:34.590 --> 00:04:37.670 think that really limited the progress.
NOTE Confidence: 0.957026033333333
00:04:37.670 --> 00:04:39.728 These were all single arm studies
NOTE Confidence: 0.957026033333333
00:04:39.728 --> 00:04:41.997 and some of them only containing
NOTE Confidence: 0.957026033333333
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
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, 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 and what are environmental factors, but what transforms some of these nine 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.
to a diagnosed instance more like in the range of maybe three to five per million per year. That tells you probably less than 1% of pancrea and urine. The consumers that are present and in patients eventually become clinically relevant. This is posing a challenge for us as we move forward. Because the increased use of imaging nowadays you can hardly go to the ER with abdominal pain without leaving the ER with a CT scan. 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,
In the past decades, you know, there have been really engaged patients. There are stories of patients who have had long histories of symptoms that went undiagnosed for decades. So there was a strive to see whether we can recognize the symptoms earlier and diagnose the cancer earlier. The challenge is the symptoms associated with these tumors are fairly vague and common in the general population. So this is the study we did from CR Medicare database. Essentially, looked at the year prior.
to their neuron cancer diagnosis,
NOTE Confidence: 0.938664642105263
what kind of doctor do they go visit and
NOTE Confidence: 0.938664642105263
what sort of symptoms do they complain of?
NOTE Confidence: 0.938664642105263
You can see, well,
NOTE Confidence: 0.938664642105263
statistically significant for most of these.
NOTE Confidence: 0.938664642105263
There are differences in
NOTE Confidence: 0.938664642105263
rates of hypertension,
NOTE Confidence: 0.938664642105263
abdominal pain, heart failure,
NOTE Confidence: 0.938664642105263
diarrhea, and peripheral edema.
NOTE Confidence: 0.938664642105263
But if you try to look at a positive
NOTE Confidence: 0.938664642105263
predictive value of these symptoms
NOTE Confidence: 0.938664642105263
when you’re in the current tumor.
NOTE Confidence: 0.938664642105263
They’re all very,
NOTE Confidence: 0.938664642105263
very low because they’re very
NOTE Confidence: 0.938664642105263
common in the general population.
NOTE Confidence: 0.920688171333333
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 group of diseases well differentiated, you’re in the consumer grade 1-2 and mainly grade 1-2 and three and they’re mostly grade 1-2 and numerically and then the essentially 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 a large scale chromosomal changes lung neuroendocrine tumor. The most common mutation seen is M and the same with pancreas M EM1.
intestinal relatively few somatic mutations,

but you see frequent loss of chromosome 18,

the poorly differential

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 know 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. So 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 you know 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. The second group, there’s loss of 1 copy of the 11 chromosomes,
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.
So what’s the link between M EMI mutation and and this and the M EMI 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 EMI. So the ATRX by itself the mutation seems to drive this phenomenon. So so 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 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 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 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 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 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

NOTE Confidence: 0.916977357272727
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 neuroendocrine tumor that has well typed Dax ATRX you see
fairly normal telomere lens and when there is Dax or a TRX alterations you see these bright pink spots which are telomere specific fish. Showing a classic pattern associated with alternative listening of telomeres, the story on essentially alternative listening telomeres and DAX ATRX mutations is actually complex in terms of prognosis. Earlier on I showed you a slide where essentially the the. Mutation of DAX ATRX and and turning out ELT was associated with good prognosis in patients with advanced pancreatic neuroendocrine tumor.
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 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 that as the tumors are 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 the same in terms of A. 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.
And since then you really have seen a lot of new agents showing activity getting FDA approved for having positive phase three trials. And I think a key thing here that happened really related to one of the meetings in Pam you were involved with. Was the first in a CTPM meeting sponsored by NCI and the importance of that meeting is really to come to consensus. What is the right kind of clinical trial design when you’re in the consumers, what are the correct endpoints? There’s a recognition progression, free survival is probably the.
right endpoint or in,

but the phase three trials

are 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

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 the systemic randomized space free trials are you know we you’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. It 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.
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
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 target some mass and receptor is PRRT, 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
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 70-80% of the cases.
when the lichen binds to
the receptor is internalized.
So.
So these agents essentially takes a
Lutetian 177 and taking into the cell
and leading 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
to neuroendocrine tumors and here you saw
a 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 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. Sunitinib was initially evaluated in a phase two study being that had two cohorts for intestinal neuroendocrine tumors and for pancreatic neuroendocrine tumors. All the responses were seen in the pancreatic neuroendocrine group. 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 a 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
toxicity was better was Bebasusan map,
there was not any significant
difference in progression free survival.
So this is probably one of
my regrets in the career.
I probably should have done this
study against placebo and we would
have had another drug available
This is what the time point in my
career where we weren’t sure whether
we can execute a placebo control trial.
It’s certainly a little bit harder to do,
but often placebo control trial
give you cleaner data.
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 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 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
00:33:26.058 --> 00:33:28.943 the lines of prior therapy Western
00:33:28.943 --> 00:33:31.580 populations would have been exposed to.
00:33:34.140 --> 00:33:36.348 Next I’m going to mention while
00:33:36.348 --> 00:33:38.592 Doctor Kunz’s trial Ecog 2211,
00:33:38.592 --> 00:33:42.705 this is actually a very important trial.
00:33:42.705 --> 00:33:45.780 Partially because the initial development
00:33:45.780 --> 00:33:48.266 of Timosolomite were essentially
00:33:48.266 --> 00:33:52.230 skipped the single agent step they were,
00:33:52.230 --> 00:33:55.178 you know most of the trials that
00:33:55.178 --> 00:33:57.130 were published were doublets.
00:33:57.130 --> 00:33:59.434 So always been a question to feel
00:33:59.434 --> 00:34:01.329 that whether you need doublets
00:34:01.330 --> 00:34:04.928 or you know where the agent is,
00:34:04.930 --> 00:34:07.990 Timosolomite by itself is a sufficient.
00:34:07.990 --> 00:34:09.434 Certainly there’s rationale to
look at this class of agents in pancreatic neuro in the consumers. If you dig back into Chuck Mattel’s papers and so forth, DTIC is active in the disease. This is a trial that compared Timosolomite to Tim Cape at the intern analysis. The study met its primary endpoint and showed improvement in progression free survival. 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 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
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 questions 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. 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, essentially takes out your kidney or makes it difficult for you receive other agents. And it may not be the best agent.

So almost certainly this is if you really want to answer this question, it needs overall survival endpoint.

Well,
00:37:35.949 --> 00:37:39.003 here’s the challenge right when for

00:37:39.003 --> 00:37:41.526 different indications you have different

00:37:41.526 --> 00:37:44.840 number of treatments available,

00:37:44.840 --> 00:37:46.640 the approved therapy for lung,

00:37:46.640 --> 00:37:49.118 there’s only ever limus in peanut you

00:37:49.118 --> 00:37:51.519 have six agents that are available,

00:37:51.520 --> 00:37:53.728 approved you can use.

00:37:53.728 --> 00:37:56.488 A 7th agents demonstrated activity

00:37:56.490 --> 00:38:00.330 that that’s probably works well.

00:38:00.330 --> 00:38:03.750 You can imagine trying to compare

00:38:03.750 --> 00:38:04.890 optimal sequences.

00:38:04.890 --> 00:38:08.810 There’s 5040 sequences,

00:38:08.810 --> 00:38:11.930 5040 arms for overall survival.

00:38:11.930 --> 00:38:14.458 This is not where we want to spend

00:38:14.458 --> 00:38:16.846 our energy and because I think

NOTE Confidence: 0.938019439166666

55
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. It will probably no longer be valid. And to give a actually example of attempt to do this, our European colleague contacted the secretor trial. The secretor trial look 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.

00:39:13.080 --> 00:39:15.996 So what did the study show?

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 Pub Med. And 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
unfavorable benefit from an exposure to medical product we environment agents.
So the bottom line is who should get this treatment is really the important
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 patient have profound benefit, but most people don’t. So what is actually the situation you are in different tumor which of these waterfall plot 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 patient all patients. Including patients who doesn’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 an 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. 

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 I 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 syntacriphy in for semester.

And like octreotide and Realty,

the prominence study actually allowed for both semester and
00:44:41.216 --> 00:44:45.284 receptor syntacrification of.

00:44:45.284 --> 00:44:53.420 And clarinet study only treated patient

00:44:53.612 --> 00:44:55.610 for semester and receptor positive.

00:44:57.930 --> 00:45:00.639 This one comes close to a predictive

00:45:00.639 --> 00:45:03.270 biomarker which is the degree of

00:45:03.270 --> 00:45:06.220 uptake and response and tumor

00:45:06.220 --> 00:45:09.730 shrinkage in in for treatment

00:45:09.730 --> 00:45:12.650 with a peptide receptor radiotherapy

00:45:12.650 --> 00:45:14.732 as you can see that comparing

00:45:14.732 --> 00:45:17.260 to the using the craning scale.

00:45:17.260 --> 00:45:18.700 As the expression goes up,

00:45:18.700 --> 00:45:21.855 the response rate increase compared

00:45:21.855 --> 00:45:24.379 for peptide receptor radiotherapy.

00:45:26.420 --> 00:45:29.738 Another biomarker that was evaluated is

00:45:29.740 --> 00:45:33.580 is more like a pharmacodynamic biomarker.

65
In early studies and single arm study, it looked like those patients who had an early drop in pomegranate had a benefit for patients treated with everolimus. But this turned out not to be that useful when we took it to phase three because the placebo patient who had a 30% dropping from Granny A also had a better outcome as well. So likely this is pointing out some issues with the assay performance and whether we're not actually have to test these patients multiple times before you get a reliable result.
00:46:17.542 --> 00:46:20.609 response is looking at profusion CT in
patients treated with veg inhibitors.

00:46:20.609 --> 00:46:22.954 We’re able to show that in patients treated
with Bebasusan app is open in a flipper

00:46:22.960 --> 00:46:25.920 set that essentially baseline parameter
and change after treatment correlated

00:46:25.920 --> 00:46:28.574 with the degree of tumor shrinkage.

00:46:28.574 --> 00:46:31.200 I think what we learned here is that
these are very difficult to do.

00:46:31.200 --> 00:46:33.994 And very operator dependent.

00:46:33.994 --> 00:46:37.078 So it’s was possible to do it in
clinical trial taking it out to the

00:46:37.080 --> 00:46:39.720 wider clinical practice is challenging.

00:46:39.720 --> 00:46:41.957 So if you look at a biomarker
landscape for neuroendocrine tumor,
you see that in terms of understanding
whether the treatment work in the in,
in the indication we do pretty well.
Whereas predictive biomarkers,
there are a few promising ones
like printing scale for
Because predictive biomarkers,
there are a few promising ones
like printing scale for
PR T&MGMT for Timoolemai,
However, we're still need a lot,
lot more work to do in terms of
So I mentioned earlier that we
have a lot of approved therapy
but most of these trial were not
designed to ask a survival question.
So you know has all this work been
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

I think we have a baseline group of

therapy that works now to find the

I think the neuron models in

and we need to obviously explore

novel therapeutic approaches.

I’ll just have two more slides

on the modeling part so.

There’s a real challenge with

developing models for well

differentiating your endocrine tumors.

There’s been many attempt 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 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, In in the the models out there, many of them highlighting yellow, have 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 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.

So what are we doing here?

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 when you’re testing,

studying new drugs or understanding the biology of Nets.
So we are using a lentivirus vector to introduce essentially doxycycline inducible alterations in key proliferation pathways. 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 or a altered P53R273 because the P53 acts as a tetramer when even one copy is actually mutated. Is in Paris it’s 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,

00:52:06.562 --> 00:52:09.750 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, so we're hoping that over the next month to year to fully characterize all the those 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, and 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 armamentarian and systemic agents where you see the evolving role?

00:54:52.229 --> 00:54:54.481 and who you work with,

00:54:54.481 --> 00:54:57.804 where you see the evolving role of surgical therapy fitting in?

00:55:00.380 --> 00:55:02.920 Depending on where you are and who you work with, what the landscape is and we have felt like surgical cyto reduction has a role in this disease.

00:55:02.920 --> 00:55:04.970 It’s complicated historically?

00:55:04.970 --> 00:55:11.327 But I I don’t know that that’s
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 have 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 is you know because the screen colonoscopy you’re finding lot of tiny rectal, you’re in the consumers which also is linked to specific race and
00:57:46.528 --> 00:57:49.055 ethnicity issues and 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.