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
Chair in the Department of GI Medicine 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 FDA approvals for pancreatic, lung and GI and other tumors. Doctor Yeah,
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 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. And during his tenure, early career and female investigators led more than 50% of the multicentered clinical trials developed through.
I've known doctor Yes since I was a fellow.

I am one of those early career investigators who benefited from his mentorship and scholarship and had the opportunity to lead one of the randomized trials through the net task force. So I'm grateful for you coming today and joining us to speak on the 2nd century of the land of small tumors. So thank you, thank you so much for that kind introduction and very glad to be here with you today. So today I'm going to talk a little bit about your endocrine tumors, 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 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 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 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 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 number, but what are environmental factors, and 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. The consumer, if you look for them compare this
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,
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 years. In the older time frame, the worst like carcinoma of 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 terminology is that this field you know at the time when these
terminologies classification created was. Relatively. 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 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, right.
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 lung neuroendocrine tumor. 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
euroendocrine 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,
some 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. So for example in pancreatic neuron different tumors, patient with high chromosomal instability.
00:13:48.960 --> 00:13:51.834 actually have a much better prognosis.
NOTE Confidence: 0.920688171333333

00:13:51.834 --> 00:13:54.199 in the advanced disease setting.
NOTE Confidence: 0.920688171333333

00:13:54.200 --> 00:13:56.279 And we’ll talk about a little bit
NOTE Confidence: 0.920688171333333

00:13:56.280 --> 00:13:58.688 in the next few slides why that
NOTE Confidence: 0.920688171333333

00:14:01.440 --> 00:14:04.000 is because it is a specific you
NOTE Confidence: 0.920688171333333

00:14:04.000 --> 00:14:06.320 know carcinogenesis pathway that’s
NOTE Confidence: 0.920688171333333

00:14:06.320 --> 00:14:09.866 this this is implying here.
NOTE Confidence: 0.920688171333333

00:14:09.866 --> 00:14:11.758 And then we see also those patients
NOTE Confidence: 0.920688171333333

00:14:11.758 --> 00:14:15.052 with intestinal neuroendocrine tumor
NOTE Confidence: 0.920688171333333

00:14:15.052 --> 00:14:17.880 with loss of chromosome 18 also have a
NOTE Confidence: 0.920688171333333

00:14:17.969 --> 00:14:20.559 not have a loss of chromosome 18
NOTE Confidence: 0.920688171333333

00:14:20.560 --> 00:14:23.446 whereas the loss of chromosome 3.
NOTE Confidence: 0.920688171333333

00:14:23.450 --> 00:14:26.708 On the lung neuron, different tumors
NOTE Confidence: 0.920688171333333

00:14:26.708 --> 00:14:29.970 pertains to a poor prognosis.
NOTE Confidence: 0.920688171333333

00:14:29.970 --> 00:14:32.914 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.
11 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 these are in Gray and in red are essentially in rich for patients with M EM1 mutations.
So what’s the link between M EM1 mutation 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
NOTE Confidence: 0.942621458823529
chromosomes and the strong association
NOTE Confidence: 0.942621458823529
between men one mutation and DAX
NOTE Confidence: 0.942621458823529
in the combination of men one DAX
NOTE Confidence: 0.942621458823529
mutation with chromosome instability.
NOTE Confidence: 0.942621458823529
So what’s going on here?
NOTE Confidence: 0.942621458823529
Why are we losing one copy of
11 chromosome and gaining on the
complementary 11 chromosomes?
NOTE Confidence: 0.942621458823529
For whatever reason,
NOTE Confidence: 0.942621458823529
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,
NOTE Confidence: 0.942621458823529
is leading to whole genome duplication.
NOTE Confidence: 0.942621458823529
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
in controlling endocrine mass.

So this is a study done at Stanford where the group looked at men and in mice doing pregnancy and you can see that men and expression goes down during pregnancy and goes back up post pregnancy. Associated with that is turning on cell cycle and increase in endocrine mass. And so there is a, you know there’s important biology here in prevention of gestational diabetes related to men in turns out is also an important regulator of telomeres.

In the Nurses in the Prostate, Lung, Colorectal Ovarian Cancer Screening
00:19:00.908 --> 00:19:03.893 Trial and Nurses Health Study that
00:19:03.893 --> 00:19:05.950 involved about 3600 patients,
00:19:05.950 --> 00:19:09.481 the group this group evaluated 743
00:19:09.481 --> 00:19:13.198 snips and try to correlate that with
00:19:13.198 --> 00:19:16.030 essentially peripheral blood telomere lens.
00:19:16.030 --> 00:19:18.638 The only gene that fell out to be
00:19:18.638 --> 00:19:20.550 important was actually men and.
00:19:20.550 --> 00:19:23.952 It was the most important implicated
00:19:23.952 --> 00:19:26.710 in control of telomere lens
00:19:26.710 --> 00:19:31.390 for for in the study.
00:19:31.390 --> 00:19:34.270 So the story of telomeres,
00:19:34.270 --> 00:19:36.694 you know as you know the telomeres are
00:19:36.694 --> 00:19:39.470 in the caps and end of our chromosomes
00:19:39.470 --> 00:19:43.070 and Menon is driving cell cycle in here.
00:19:43.070 --> 00:19:45.765 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 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
00:20:35.120 --> 00:20:39.165 there is Dax or a TRX alterations
00:20:39.165 --> 00:20:42.169 you see these bright pink spots
00:20:42.169 --> 00:20:45.169 which are telomere specific fish.
00:20:45.170 --> 00:20:49.600 Showing a classic pattern associated
00:20:49.600 --> 00:20:53.130 with alternative listening of telomeres,
00:20:55.450 --> 00:20:59.076 the story on essentially alternative
00:20:59.076 --> 00:21:02.294 listening telomeres and DAX ATRX mutations
00:21:02.294 --> 00:21:06.088 is actually complex in terms of prognosis.
00:21:06.090 --> 00:21:09.282 Earlier on I showed you a slide
00:21:09.282 --> 00:21:11.476 where essentially the.
00:21:11.476 --> 00:21:16.508 Mutation of DAX ATRX and and turning
00:21:16.508 --> 00:21:19.202 out ELT was associated with good
00:21:22.357 --> 00:21:24.526 pancreatic neuroendocrine tumor.
The situation is actually reversed in the earlier disease.

Essentially what’s going on is that advanced disease the the DAX ATRX mutation.

Is marking a group of pancrea urine 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.

So these are patients with familial mutations in M EM1.

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

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 in patients

were relatively newly diagnosed with

small bowel neuroendocrine tumor.

They were able to demonstrate

improvement progression free survival.

A similar trial was land Realty

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 subseuent 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 PRRT, which really has become very well, widely used at this point. Again, in the earlier development of PRRT it was not.
in 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
00:28:22.084 -- 00:28:25.130 2 when the lichen binds to
NOTE Confidence: 0.847688196363636
00:28:25.130 -- 00:28:27.138 the receptor is internalized.
NOTE Confidence: 0.847688196363636
00:28:27.140 -- 00:28:27.806 So.
NOTE Confidence: 0.847688196363636
00:28:27.806 -- 00:28:31.615 So these agents essentially takes a
NOTE Confidence: 0.847688196363636
00:28:31.615 -- 00:28:34.940 Lutetian 177 and taking into the cell
NOTE Confidence: 0.847688196363636
00:28:34.940 -- 00:28:37.298 and leading to very good efficacy.
NOTE Confidence: 0.95132334
00:28:40.790 -- 00:28:43.838 There's also a role for targeted
NOTE Confidence: 0.95132334
00:28:43.838 -- 00:28:45.870 therapy in neuroendocrine tumors.
NOTE Confidence: 0.95132334
00:28:45.870 -- 00:28:48.814 One of the drugs that we were involved
NOTE Confidence: 0.95132334
00:28:48.814 -- 00:28:51.007 in developing is everolimus of
NOTE Confidence: 0.95132334
00:28:51.007 -- 00:28:53.542 affinitor targeting the emptor pathway.
NOTE Confidence: 0.95132334
00:28:53.542 -- 00:28:57.167 The Radian 3 trial was the first
NOTE Confidence: 0.95132334
00:28:57.167 -- 00:29:02.742 to report out and for pancreatic
NOTE Confidence: 0.95132334
00:29:02.742 -- 00:29:09.710 neuroendocrine tumors and here you saw
NOTE Confidence: 0.95132334
00:29:09.710 -- 00:29:27.806 a benefiting progression free survival
NOTE Confidence: 0.95132334
00:29:27.806 -- 00:29:34.940 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. 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. 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
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
for neuroendocrine much earlier on.

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 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, this 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 whether you need doublets that whether you need doublets or you know where the agent is, Timosolomite by itself is a sufficient.
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. So 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
00:35:36.494 --> 00:35:39.218 around agents that targets these.
NOTE Confidence: 0.938019439166666
00:35:39.218 --> 00:35:42.382 These are stable or early disease like
NOTE Confidence: 0.938019439166666
00:35:42.382 --> 00:35:45.263 TRILTY and then Realty in the pro
NOTE Confidence: 0.938019439166666
00:35:45.263 --> 00:35:48.896 Med and the CLARINET study and in the
NOTE Confidence: 0.938019439166666
00:35:48.896 --> 00:35:52.433 studies who tend to target patients
NOTE Confidence: 0.938019439166666
00:35:52.433 --> 00:35:55.464 was faster progressing disease PRT
NOTE Confidence: 0.938019439166666
00:35:55.464 --> 00:35:57.588 somewhere in the middle that required
NOTE Confidence: 0.938019439166666
00:35:57.588 --> 00:35:59.720 progression in the past three years.
NOTE Confidence: 0.938019439166666
00:35:59.720 --> 00:36:02.246 And most of the targeted agents
NOTE Confidence: 0.938019439166666
00:36:02.246 --> 00:36:04.615 require progression in the past one
NOTE Confidence: 0.938019439166666
00:36:04.615 --> 00:36:07.055 year when in the case of Radian 4
NOTE Confidence: 0.938019439166666
00:36:07.128 --> 00:36:09.960 progression within the past six months.
NOTE Confidence: 0.938019439166666
00:36:09.960 --> 00:36:12.592 So what are some of the remaining
NOTE Confidence: 0.938019439166666
00:36:12.592 --> 00:36:14.412 challenges and questions that we
NOTE Confidence: 0.938019439166666
00:36:14.412 --> 00:36:16.589 we have when you’re in the current
NOTE Confidence: 0.938019439166666
00:36:16.589 --> 00:36:17.880 tumor at this point,
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. 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 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 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
to try OS as the primary endpoint.

They were going to look at FS2.

So initially are due to a cruel

issues that they had to do scale

back their ambitions to look at

FS1 as the primary endpoint.

So what did the study show?

Yeah, actually showed that although

Streptozosin set of toxic chemotherapy.

Was a little bit more toxic but higher,

had a higher response rate,

but there was no difference in progression

free survival between the two arms.

So higher higher response rate may not

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 or worse 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 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 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. 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 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 IHC? 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. 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, 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 octreotile 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.
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,
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 actually not to be useful when we took it to phase three because the placebo patient also had a better outcome as well. Likely this is pointing out some issues with the assay performance and whether we actually have to test these patients multiple times before we get a reliable result. 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 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 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 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 genetically engineered patient derived organoid models. We know that if you alter P53 or Rv, these things will grow 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 lenty 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 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
You can do this. You can directly in fact the primary cells, you can grow them in organizing. In fact the organize and what’s the right condition and how to solve this work. 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, so we're hoping that over the next month to year to fully characterize all these 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 patients will benefit from 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?
NOTE Confidence: 0.950317
00:54:43.284 --> 00:54:43.420 Yeah.
NOTE Confidence: 0.950317
00:54:43.420 --> 00:54:43.620 Kevin,
NOTE Confidence: 0.951994
00:54:47.340 --> 00:54:48.939 thanks. Doctor Yellen,
NOTE Confidence: 0.951994
00:54:48.939 --> 00:54:52.229 can you comment given the expanding
NOTE Confidence: 0.951994
00:54:52.229 --> 00:54:54.481 armamentarian and systemic agents
NOTE Confidence: 0.951994
00:54:54.481 --> 00:54:57.804 where you see the evolving role
NOTE Confidence: 0.951994
00:54:57.804 --> 00:55:00.380 of surgical therapy fitting in?
NOTE Confidence: 0.951994
00:55:00.380 --> 00:55:02.920 Depending on where you are
NOTE Confidence: 0.951994
00:55:02.920 --> 00:55:04.970 and who you work with,
NOTE Confidence: 0.951994
00:55:04.970 --> 00:55:11.327 felt like surgical cyto reduction
NOTE Confidence: 0.951994
00:55:11.327 --> 00:55:15.062 has a role in this disease.
NOTE Confidence: 0.951994
00:55:15.062 --> 00:55:21.534 But I don’t know that that’s
NOTE Confidence: 0.951994
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,
So I think there’s still room to use more modality including surgery and international radiology techniques 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
NOTE Confidence: 0.918433135
from the bulking all types
NOTE Confidence: 0.954789557777778
should there’s an increase in
NOTE Confidence: 0.954789557777778
incidence but also survival.
NOTE Confidence: 0.954789557777778
Are you able to kind of differentiate
increased diagnosis of otherwise
ability versus advances in therapy
or you know parse this out? Yeah.
NOTE Confidence: 0.954789557777778
So I think one of the ways we’re looking
at the survival changes is limiting our
analysis to those with metastatic disease.
NOTE Confidence: 0.954789557777778
There are still very much some limitations
when you look at that sort of data.
NOTE Confidence: 0.954789557777778
But I think the large registry is
probably still the best way to look
NOTE Confidence: 0.954789557777778
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 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
ethnicity issues and in in small
pancreatic urine the consumer is going to be something we're going
to have to deal with just the increase CT start getting done.
Well, thank you so much Doctor Yao for coming today.