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 Medical Oncology at the University of MD Anderson Cancer Center, and he received his medical degree from Baylor College of Medicine and completed his fellowship at MD Anderson. So for the last two decades, Dr. Yao and colleagues have really transformed the field of neuroendocrine tumors. So that is how I know him and he has led practice changing randomized clinical trials, specifically the family of radiant clinical trials that include the drug everolimus, that led to FD approvals for pancreatic net, lung net and GI and undercon tumors.
I was also a strong advocate of mentoring and education. He is a founding member and past chairman of the North American Neuroendocrinic Tumor Society of which I am the president of this year. And then through that society can helped establish two young investigator awards that fund early career investigators. He’s also the past chair of the NCIA and under consumer task force. And during his tenure, led more than 50% of the multicentered clinical trials developed through the society.
that net task force.

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, and joining us to speak on the 2nd century of the land of small tumors.

So thank you,
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 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 century where we’ve learned a lot about the Natural History of the disease. Understand a lot of the endocrine manifestations of neuroendocrine tumors and we also learn a lot about epidemiology of disease in semester biology. However, the number of therapeutic introduced over this period is actually relatively sparse prior to I would say the more recent approvals. There was only one drug that was FDA approved for oncologic control and that streptosis dosen for pancreatic net. There were two drugs approved for hormonal control of the neuroendocrine tumors.
This is certainly not for lack of effort. This is a classic lecture by Chuck Mortell where he talks about his odyssey in the land of small tumors as you can see on the table on the right. There’s been numerous agents that were studied but these chemotherapy agents did not really have that much activity with the exception of DTIC and streptozosin in pancreatic neuroendocrine tumors. Another thing you’ll see is that because you know this disease was thought to be rare and he that’s why he used the term land.
of small tumors. The studies were actually very small and I think that really limited the progress. These were all single arm studies and some of them only containing less than a handful of patients. So one of the first things I think we needed to understand about neuroendocrine tumors is that the disease is probably actually more common than we think. One of the analysis we did in from the SEAR database and we showed that comparing to other malignant neoplasms diagnose incidence of neuroendocrine tumor is continually rising and since this we have a kind of updated the data.
and in you know when when it was in 2004 the incident was about 5 per 100,000, 2012 about the.

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 into a subtypes that will remain. Rare for quite a quite a long time. One of the question to think about is, was this rising incidence and so forth is what’s going on here. There are environmental factors that are increasing the incidence of
neuroendocrine tumor or perhaps this is just better recognition of the disease. Certainly we are seeing more neuroendocrine tumors in some case related in the gastric urine the consumer. Related to use of PPI's, but I think for the most part these neuroendocrine tumor has always been there. So here are a couple of classic studies in two in, studies in two in, in Carcino tumors are really talking about intestinal neuroendocrine tumors are two studies that included 15,000 autopsies and these tumors
00:07:14.850 --> 00:07:18.380 are found in about 1% of autopsies.
NOTE Confidence: 0.930937682962963
00:07:18.380 --> 00:07:21.050 So these are patient who died
NOTE Confidence: 0.930937682962963
00:07:21.050 --> 00:07:22.560 from unrelated causes.
NOTE Confidence: 0.930937682962963
00:07:22.560 --> 00:07:25.871 And most mostly lift out their natural
NOTE Confidence: 0.930937682962963
00:07:25.871 --> 00:07:28.520 lifespan without having them diagnosed.
NOTE Confidence: 0.930937682962963
00:07:28.520 --> 00:07:31.285 So really the question is not so
NOTE Confidence: 0.930937682962963
00:07:31.285 --> 00:07:34.800 much whether they’re increasing in
NOTE Confidence: 0.930937682962963
00:07:34.800 --> 00:07:36.680 and what are environmental factors,
NOTE Confidence: 0.930937682962963
00:07:36.680 --> 00:07:39.760 but what transforms some of these nine
NOTE Confidence: 0.930937682962963
00:07:39.760 --> 00:07:42.656 small tumor into malignant ones but
NOTE Confidence: 0.930937682962963
00:07:42.656 --> 00:07:44.160 pancreatic neurin different tumors.
NOTE Confidence: 0.930937682962963
00:07:44.160 --> 00:07:46.600 There’s one study that was in Hong Kong,
NOTE Confidence: 0.930937682962963
00:07:46.600 --> 00:07:51.070 again 11,000 autopsy one in 1000.
NOTE Confidence: 0.930937682962963
00:07:51.070 --> 00:07:53.428 Autopsy specimen had a pancreatic urine.
NOTE Confidence: 0.930937682962963
00:07:53.428 --> 00:07:54.218 The consumer,
NOTE Confidence: 0.930937682962963
00:07:54.218 --> 00:07:56.944 if you look for them compare this
to a diagnosed instance more like
in the range of maybe three to five
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
00:08:33.450 --> 00:08:34.635 pancreatic neuroendocrine tumors,
NOTE Confidence: 0.938664642105263
00:08:34.635 --> 00:08:37.789 some of them in the head of pancreas
NOTE Confidence: 0.938664642105263
00:08:37.789 --> 00:08:40.642 where if you try to operate on them may,
NOTE Confidence: 0.938664642105263
00:08:40.650 --> 00:08:42.596 may, may be a quite a morbid
NOTE Confidence: 0.938664642105263
00:08:42.596 --> 00:08:44.130 and higher risk procedure.
NOTE Confidence: 0.938664642105263
00:08:44.130 --> 00:08:47.210 So understanding which of these can be
NOTE Confidence: 0.938664642105263
00:08:47.210 --> 00:08:50.180 left alone and patients are going to.
NOTE Confidence: 0.938664642105263
00:08:50.180 --> 00:08:51.560 Essentially lived with disease.
NOTE Confidence: 0.938664642105263
00:08:51.560 --> 00:08:52.940 in their natural lifespan,
NOTE Confidence: 0.938664642105263
00:08:52.940 --> 00:08:55.306 which one is near to near that
NOTE Confidence: 0.938664642105263
00:08:55.306 --> 00:08:57.668 really needs to intervene on is
NOTE Confidence: 0.938664642105263
00:08:57.668 --> 00:09:00.212 going to be important going forward.
NOTE Confidence: 0.938664642105263
00:09:00.220 --> 00:09:03.668 So the other thing that the with you know
NOTE Confidence: 0.938664642105263
00:09:03.668 --> 00:09:05.748 this information about the incidence
NOTE Confidence: 0.938664642105263
00:09:05.748 --> 00:09:08.180 and prevalence in your endocrine tumors
NOTE Confidence: 0.938664642105263
00:09:08.180 --> 00:09:11.978 is that the patient advocacy groups,
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 there was a strive to see whether we can recognize the symptoms earlier and diagnose the cancer earlier. But the challenge is the symptoms that are associated with these tumors are fairly vague and common in the general population. So this is study we did from CR Medicare database. Essentially, looked at the year prior.
to their neuron cancer diagnosis, what kind of doctor do they go visit and what sort of symptoms do they complain of? You can see, well, statistically significant for most of these. There are differences in rates of hypertension, abdominal pain, heart failure, diarrhea, and peripheral edema. But if you try to look at a positive predictive value of these symptoms when you’re in the current tumor. They’re all very, very low because they’re very common in the general population. The newer endocrine field also is
a field where the very terminology we or she used to describe the disease has been evolving in the over the past decades. In the older time frame, the worst like carcinoey 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
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. The most common mutation seen is M and the same with pancreas. But here you also see DAX and ATRX and...
intestinal relatively few somatic mutations,
but you see frequent loss of chromosome 18,
the poorly differential neuro endocrine tumor.
It’s probably really a mixed bag a lot of time these are essentially transformed versions of adenocarcinoma,
transformed lower grade tumor after certain types of therapy,
but they’re characterized by a very fast growth rate and mutation in TP53 and RV are the most common mutations.
So if you understand the genomics of neuroendocrine tumors,
so one of the things we did is leverage our large phase three clinical trials.

We did a series of trials called radium trials looking at everolimus where over about 1000 patients across you. Four studies were enrolled and where we can get the tumor. We did a whole genome analysis. We saw relatively few somatic mutations, but what is striking is the amount of largescale chromosomal changes that you see chromosomal gain and chromosomal loss and these actually have very significant prognostic value. For example in pancreatic 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
00:13:58.688 --> 00:14:01.440 is because it is a specific you 
NOTE Confidence: 0.920688171333333
00:14:01.440 --> 00:14:04.000 know carcinogenesis pathway that’s 
NOTE Confidence: 0.920688171333333
00:14:04.000 --> 00:14:06.320 this this is implying here. 
NOTE Confidence: 0.920688171333333
00:14:06.320 --> 00:14:09.866 And then we see also those patients 
NOTE Confidence: 0.920688171333333
00:14:09.866 --> 00:14:11.758 with intestinal neuroendocrine tumor 
NOTE Confidence: 0.920688171333333
00:14:11.758 --> 00:14:15.052 with loss of chromosome 18 also have a 
NOTE Confidence: 0.920688171333333
00:14:15.052 --> 00:14:17.880 far better prognosis than those who do 
NOTE Confidence: 0.942621458823529
00:14:17.969 --> 00:14:20.559 not have a loss of chromosome 18 
NOTE Confidence: 0.942621458823529
00:14:20.560 --> 00:14:23.446 whereas the loss of chromosome 3. 
NOTE Confidence: 0.942621458823529
00:14:23.450 --> 00:14:26.708 On the lung neuron, different tumors 
NOTE Confidence: 0.942621458823529
00:14:26.708 --> 00:14:29.970 pertains to a poor prognosis. 
NOTE Confidence: 0.942621458823529
00:14:29.970 --> 00:14:32.914 So one of the things that really always
short struck me is really what’s going on with pancreatic neural in the consumer. It’s really one of my favorite diseases in the sense there’s so much, so much stuff here. So you see here when we sequence the pancreatic neural in the tumors. They roughly fall into three categories when you look at the host whole genome in terms of chromosomal changes. In the first group here, Group One, they lose one copy of 11 of the 22 chromosomes. In the second group, there’s loss of 1 copy of the 11 chromosomes,
one copy of 11 chromosomes.

And gain on the complementary 11 chromosomes and then there's a group that are relatively stable in terms of chromosomal abnormalities.

And on the bottom panel is little small. So I'll just talk through it a little bit and it’s important in the sense that you can actually link these chromosomal changes to specific mutations that are present in if you look at this.

The chromosomal instability tumors are in Gray and in red are essentially are in rich for patients with M EM1 mutations.
So what’s the link between M EM1 mutation and this and the M EM1 mutations is also linked with DAX whereas the ATRX mutations. Essentially also involved in alternative links. Near telomeres can be associated with chromosome instability in absence of M EM1. So the ATRX by itself the mutation seems to drive this phenomenon. So what we see here is then you see DAX and ATRX mutations associated chromosomal instability. And you have, you know loss of 1 copy of 11 chromosome
and gain on the complementary 11 chromosomes and the strong association between men one mutation and DAX in the combination of men one DAX mutation with chromosome instability.

So what’s going on here? Why are we losing one copy of 11 chromosome and gaining on the complementary 11 chromosomes? For whatever reason, you’re essentially what’s actually going on is you’re losing one copy of 11 chromosomes and this in some patients, probably due to happily insufficiency, is leading to whole genome duplication. So essentially these are copy neutral LOH.
They are occurring essentially in the game because the whole genome duplication. Is occurring in the complementary 11 chromosomes. So what’s the story here? While the most common mutation in your endocrine tumor is man one specifically endocrine tumor is man one specifically linked to pancreatic neuroendocrine tumors occurring roughly about 40% of patients and also associated with lung neuroendocrine tumors. What do we know about man one biology? It is certainly is epigenetic regulators involved in modulating P27 and it’s actually involved
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
Tri and Nurses Health Study that involved about 3600 patients, the group this group evaluated 743 snips and try to correlate that with essentially peripheral blood telomere lens. The only gene that fell out to be important was actually men and. It was the most important implicated in control of telomere lens for for in the study. So the story of telomeres, you know as you know the telomeres are in the caps and end of our chromosomes and Menon is driving cell cycle in here. The telomere lens is going to get
short as telomere lens gets short.

Essentially usually the cancer cell dies where you need to turn 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 lising 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 A TRX 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 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 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, one families.

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 get 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 sections 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 tumor 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
probably about two to 3000 patients
and probably 8 to 10 years to execute.
So that’s why you will see
in the subsequent slide most of
the approved agents are able to
then demonstrate PFS benefit.
But we don’t have quite a
large sample size needed that
demonstrates survival benefit
00:25:02.050 --> 00:25:04.492 going going into the the systemic
NOTE Confidence: 0.9456722469230777
00:25:04.492 --> 00:25:06.762 randomized space free trials are you
NOTE Confidence: 0.9456722469230777
00:25:06.762 --> 00:25:09.066 know we you’re going to talk to them
NOTE Confidence: 0.9456722469230777
00:25:09.141 --> 00:25:11.565 a little bit about different targets.
NOTE Confidence: 0.9456722469230777
00:25:11.570 --> 00:25:13.598 So the first targets we’ll talk
NOTE Confidence: 0.9456722469230777
00:25:13.598 --> 00:25:15.610 about is the Smestan receptor.
NOTE Confidence: 0.9456722469230777
00:25:15.610 --> 00:25:18.884 For a long time prior to this Smestan
NOTE Confidence: 0.9456722469230777
00:25:18.884 --> 00:25:21.580 receptor targeting was Octreotype.
NOTE Confidence: 0.9456722469230777
00:25:21.580 --> 00:25:24.016 Was approved for control of Carson
NOTE Confidence: 0.9456722469230777
00:25:24.016 --> 00:25:26.453 syndrome it relief flushing and diarrhea
NOTE Confidence: 0.9456722469230777
00:25:26.453 --> 00:25:28.858 in probably about 70% of the patients.
NOTE Confidence: 0.9456722469230777
00:25:28.858 --> 00:25:31.415 But there are a lot of back and
NOTE Confidence: 0.9456722469230777
00:25:31.415 --> 00:25:33.461 forth debate as to whether actually
NOTE Confidence: 0.9456722469230777
00:25:33.461 --> 00:25:36.450 or not is slow cancer grows and it
NOTE Confidence: 0.9456722469230777
00:25:36.450 --> 00:25:38.580 was almost like a little religion
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people either believe it or we they didn’t but what was important is you just need to actually do the trial it turns out and in this phase three trial that’s done by the. A multicenter German trial in 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 subsequent publications and analysing analysis of popular population of studies that can demonstrate while when you terminate a study 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 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. Specifically for semastin receptor
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 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 overall survival benefit. Another targeted agent that’s shown benefit is sunitinib. So Sunita was initially evaluated in a phase two study with 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 was significant benefit.
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 the agent is.
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
DNA repair pathway when that often are methylated MGMT and leading to low expression and you can see. That for patients with low MGMT, the response rate is much higher than those who have intact MGMT expression. So if you look at the current treatment landscape for neuroendocrine tumor, we have come a long way. You know in the beginning historically we only have one agent for pancreatic net. Now you have number of phase three clinical trial covering many of the different in your endocrine tumors. Essentially these are clustered.
around agents that targets these.
These are stable or early disease like TRILTY and then Realty in the pro Med and the CLARINET study and in the studies who tend to target patients was faster progressing disease PRT somewhere in the middle that required progression in the past three years. And most of the targeted agents require progression in the past one year when in the case of Radian 4 progression within the past six months. So what are some of the remaining challenges and questions that we have when you’re in the current tumor at this point,
one of the 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. Because 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 an example of attempt to do this, our European colleague contacted the secretor trial. The secretor trial looks 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 PFS2. So initially are due to a cruel issue that they had to do scale back their ambitions to look at PFS1 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 PubMed, you’ll get thousands, probably near 10,000 results back. So what do we know about biomarkers for neuroendocrine tumors? I usually think about biomarkers as two classes. These are prognostic identifying those people who have a better outcome and predictive meaning to actually sorting out individual who are more likely.
But then similar individual without a biomarker to experience a favorable 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

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 a efficacy of biomarker population which means we only essentially randomize a efficacy of biomarker population which means we only essentially randomize.
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 classic example in colon cancer is cetuximab.

The initial FDA approval in clinical trial was for patients.

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

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

And the net example is really kind
00:43:16.355 --> 00:43:19.000 something I kind of lived through.

00:43:19.000 --> 00:43:21.275 After we started a phase three trial,

00:43:21.280 --> 00:43:23.476 a publication came out in science

00:43:23.480 --> 00:43:26.756 showing about 15% of the patients with

00:43:26.756 --> 00:43:30.248 pancreatic net at M Tor pathway mutations.

00:43:30.250 --> 00:43:32.170 So I I I will,

00:43:32.170 --> 00:43:35.014 I would gladly admit I was a very lucky

00:43:35.014 --> 00:43:38.203 not to know that when I started the trial.

00:43:38.210 --> 00:43:41.586 But because it turns out you

00:43:41.586 --> 00:43:43.730 know extra pancreatic net,

00:43:43.730 --> 00:43:45.530 none of the patients have

00:43:45.530 --> 00:43:46.610 mtor pathway mutations,

00:43:46.610 --> 00:43:48.686 quote mtor pathway mutations,

00:43:48.686 --> 00:43:52.490 but they all benefited from the therapy

00:43:52.490 --> 00:43:55.325 and even in the pancreatic net group

NOTE Confidence: 0.941691228571429
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.
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 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 also whether we’re not actually have to test these patients multiple times before you get a reliable results. Another BOW marker attempting to look at the predictive bow marker in terms of
response is looking at profusion CT in patients treated with veg inhibitors. We're able to show that in patients treated with Bebasusan app is open in a flipper set that essentially baseline parameter and change after treatment correlated with the degree of tumor shrinkage. I think what we learned here is that these are very difficult to do. And very operator dependent. So it's was possible to do it in clinical trial taking it out to the wider clinical practice is challenging. So if you look at a biomarker landscape for neuroendocrine tumor,
you see that in terms of understanding whether the treatment work in the indication we do pretty well. Whereas predictive biomarkers, there are a few promising ones like printing scale for PR T&MGMT for Timosolemai, However, we're still need a lot, 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 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.
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.
There are models out there, but many of them are altering in such a fundamental way that I don’t think they represent your end of biology. So if you look at the published cell lines and, many of them highlighting yellow, 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 the neuroendocrine slow growing biology. So how do we tackle this? One of the efforts we’ve been doing in our lab is using a genetically engineered patient derived organo way models. We know that if you alter P53 or RV. These these things will grow and take and proliferate, but you don’t want the P53RB L you know altered when you’re testing, studying new drugs or understanding the biology of Nets.
So we are using a lentivirus 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 an altered P53R273 because the P53 acts as a tetramer when even one copy is actually mutated. Is in Paris its function still a lot of work to do to
00:51:53.258 --> 00:51:54.936 figure this out because there
are many different variations.

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

00:52:01.010 --> 00:52:02.570 you can grow them in organizing.

00:52:06.562 --> 00:52:09.750 condition and how to solve this work.

00:52:09.750 --> 00:52:11.100 We’re happy to show that
we’re making progress,

00:52:11.910 --> 00:52:15.247 that we can actually use the system to
make your endocrine tumor organoids grow

00:52:20.150 --> 00:52:22.148 because the previous attempts to organize,

00:52:23.590 --> 00:52:25.030 factor to keep them alive,

00:52:25.030 --> 00:52:26.170 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.
00:53:11.390 --> 00:53:11.470 You can say it there. Any questions from the audience or from online, maybe one, see if anyone in the chat,

00:53:34.240 --> 00:53:35.680 I'll ask the first question,

00:53:35.680 --> 00:53:40.799 what are you most excited about from a therapeutic standpoint in the next decade?

00:53:41.920 --> 00:53:44.600 That's a tough question. You know I I think there's still a role for immunotherapy but probably not with existing checkpoint inhibitors but maybe within except for maybe subpopulations.

00:53:51.988 --> 00:54:00.170 That's one of the things we're learning is although tumor mutational burden is generally low,
you’re in the patients live a long time.

So that tumor mutation burden actually may change over time.

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

So that’s actually I think the relevant sequencing question. When you use that early, does that mean later on they have a high T MB and you can go back with I/O,
00:54:42.740 --> 00:54:43.284 that sort of things?

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

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

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

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

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

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

00:55:00.380 --> 00:55:02.920 Depending on where you are

00:55:02.920 --> 00:55:04.970 and who you work with,

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

00:55:11.327 --> 00:55:15.062 felt like surgical cyto reduction

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

00:55:18.606 --> 00:55:21.534 But I I don’t know that that’s
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 technique and so forth. The surgery of symptoms, it certainly can mean, yeah, you know there's many different ways it can in you know some cases patients have essentially abdominal discomfort from a local tumor with nodes and the surgical resection will bypass can be very important for them even though palliative and patients who have. Severe Carson syndrome sometime.
refractive therapy and benefit
from the bulking all types
should there’s an increase in incidence but also survival.
Are you able to kind of differentiate increased diagnosis of otherwise ability versus advances in therapy or you know parse this out? Yeah.
So I think one of the ways we’re looking at the survival changes is limiting our analysis to those with metastatic disease. There are still very much some limitations when you look at that sort of data. But I think the large registry is probably still the best way to look at the survival data because when
you look at individual institutions, you have a lot of referral bias. You know, those patients who has surgery are cured, they don't come to tertiary centers, right. They're going on and living their normal lives. And so the large registry still have a very important role there. And the increase in incidence is happening in distinct areas like rectal is you 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.