It is. My name is Pam Koons.

I’m a GI medical oncologist and the director of the Center for GI Cancers.

It’s my great pleasure to get to introduce Doctor Kiran Taraga as today’s speaker and welcome to those in person and everybody online.

So Doctor Traga is a professor of surgery and the division Chief of Surgical Oncology in the Department of Surgery and the Assistant medical director for the Clinical Trials Office.

At Yale Cancer Center,
he joined Yale in fall of 22, and I'm from the University of Chicago, where he was vice chief of the section of General Surgery and Surgical Oncology and director of the surgical GI Cancer program. He is considered a national, international thought leader in the management of Oligometastatic disease and is an expert in regional perfusion, including hyperthermic intraperitoneal chemotherapy or hypec. This is a technique that delivers chemotherapy intraperitoneally following resection of visible tumors and his research focuses in...
this space specifically on clinical trials exploring the interface of immunotherapy and liquid biopsy and the surgical management of cancers. I can say personally it’s been really wonderful to have you here, Karen and he is a fantastic collaborator for the scientists. I’m putting in a plug that he is looking for potential partners. So I’m. So Karen, thank you for joining us today, Doctor Koons and
thank you everyone for coming today. I took the liberty to of sharing some slides which have some of our research interests. And so forgive me if it seems like there’s just so many topics we’re covering it just we’ll hopefully share with you how excited I am about this field and how much I would love to get all of you excited about it as well. Renee, do you know if I can turn some of the lights down around this space here? Because I think I have some videos I was running here. So I am a surgeon and it is
lunchtime and I do apologize.

I'm going to show some pictures.

I tried to kind of reduce the number of pictures I have.

do consult for I've just done some consulting for Mark, but it’s not anything I’m going to speak about today.

So in 2016 there was this news frenzy that I’m sure most of you probably didn’t even see, but it said a new organ has been discovered.
the peritoneum and the mesentery.

And so for all of us surgeons in the room we laughed because you know this is something people have known for thousands of years.

But I think what you’re seeing in this schematic over here is you’re seeing the colon. So you can see in the panel C here, maybe I’ll just move my mouth so everyone can see it.

So in the panel C, you can sort of see how the mesentery kind of wraps around the colon. And I tell patients the peritoneum
NOTE Confidence: 0.9301902
00:03:16.612 --> 00:03:18.670 is just sort of like a membrane,
NOTE Confidence: 0.9301902
00:03:18.670 --> 00:03:20.866 which is essentially like Saran wrap.
NOTE Confidence: 0.9301902
00:03:20.870 --> 00:03:23.264 It’s essentially as thin as Saran wrap,
NOTE Confidence: 0.9301902
00:03:23.270 --> 00:03:24.986 but it has some remarkable functions.
NOTE Confidence: 0.9301902
00:03:24.990 --> 00:03:26.550 It it has, you know,
NOTE Confidence: 0.9301902
00:03:26.550 --> 00:03:29.126 it clears a lot of endotoxins,
NOTE Confidence: 0.9301902
00:03:29.126 --> 00:03:30.494 bacteria, there’s macrophages,
NOTE Confidence: 0.9301902
00:03:30.494 --> 00:03:33.230 there’s some T cells in that.
NOTE Confidence: 0.9301902
00:03:33.230 --> 00:03:35.370 It has very important roles
NOTE Confidence: 0.9301902
00:03:35.370 --> 00:03:36.654 in cellular adhesions.
NOTE Confidence: 0.9301902
00:03:36.660 --> 00:03:38.256 And so it’s a very interesting thing.
NOTE Confidence: 0.9301902
00:03:38.260 --> 00:03:39.755 And as surgeons we notice
NOTE Confidence: 0.9301902
00:03:39.755 --> 00:03:41.250 this because cancers when they
NOTE Confidence: 0.9301902
00:03:41.309 --> 00:03:43.019 spread to the peritoneal lining,
NOTE Confidence: 0.9301902
00:03:43.020 --> 00:03:45.420 they rarely cross the peritoneal barrier.
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7
So it's a very interesting phenomenon that such a thin membrane can actually restrict tumors within this membrane. And so it's a very exciting sort of space to think about. And you know the biggest question is always you know, where do peritoneal surface malignancy stand and should we club all of them together like. Is the phenotypic expression of metastasis as the peritoneal metastases, is that more important or do we think of cancer is more like gastric cancer, pancreatic cancer, liver cancer?
And so is it more Histology specific in terms of where they start or the phenotypic expression? And I would argue that it is a combination of both. So I think clearly you have to recognize Histology specific, you have to think about the somatic mutations, you have to think about what the primary tumor is. The tumors that spread to the peritoneum are somewhat bound by some general common principles, some which is that they tend to spread.
in a very different way than hematogenous or lymphatic spread. So they rarely spread, you know, beyond sort of these spaces and they spread by almost contact. It’s a very bizarre phenomenon when we open the abdomen and we look. It’s always in spaces which are sort of sequestered where the flow of peritoneal fluid gets stopped. So the right diaphragm for instance or by the ligament of trite, so just a very mechanical sort of a problem that we see. And in this talk when we’re talking
about peritoneal metastasis, you know generally we’re thinking of secondary peritoneal tumors, so tumors that have started at another site and then spread to the peritoneum even though there are primary peritoneal malignancies like mesothelioma or decimal plastic small round cell tumors. That occur in the peritoneum itself. Now the question is how do we estimate the incidence of this? Is this a big problem or is this a very small problem? And the answer is we don’t exactly
know how big the problem is.

But I would contend and we’ve done the math on this and we’ve kind of looked at this annually there’s probably about 100 to 150,000 patients with peritoneal metastases that are diagnosed every year. If you add up everyone that’s a lot, that’s about three times the number of new pancreas cancer diagnosis every year. So it it is something phenotypically is a very large but heterogeneous population.

So those of you that have heard this talk, you know or heard some version of my talk have seen this slide, but I don’t,
I won’t apologize for it because I do think this was a very important part in my life in deciding how and why to do para new metastasis. And this was a young patient who had colon cancer and had clean scans and presented with a bowel obstruction. And I explored his abdomen over here and and for you know, those of you in the room, what we’re seeing here, you know, this is the liver, this is the head of the patient. You can see the graphic there, the liver right.
there, the transfer of stolen

And the sheet of Elmer’s glue,

that was his peripheral metastasis and.

And it was very unfortunate that we just could not help this young patient who then succumbed to this cancer in a few months after this.

So. So it’s a, it was a very thought provoking problem that I have dedicated my career to.

And so First off, I would just say that peritoneum metastases are much more common than we think they are.
And and why is that? Well, think about it this way if you cannot. Detected on CT scans or PET scans or MRI's, you cannot actually measure it. So in this, in this graphic that one of our residents made many years ago, we just looked at all the different sort of sources of incidence of peritoneal metastases. And if you look at the NCCN text, which comes from randomized trials which require resist measurable tumor, which means you should be able to measure the tumor, the incidence only seems 2% or 3%.
But if you actually look at autopsy series, which are dominated by patients probably who die of different reasons, but when you look in that, the incidence of metastasis is as much as 20%. And this is only for colon cancer. So I imagine 135,000 new colon cancers a year, and you have 20% of them with peritoneal metastasis. And if they’re mucinous tumors, it’s 40%. So it’s a much higher incidence. But the problem is we don’t know where the reality is. Because we don’t know how to
measure pelvic metastasis.

So that's one of the big problems and challenges that are there.

I think the second is that these patients don't have clinical trials for them often. Why?

Because we can't measure it. If you can't measure it, there's no drug company that's willing to give you a drug to put these patients on clinical trials because you don't have measurable disease. So how do you know if your drug is working or not? And that's the biggest challenge we all face.
And in fact, this is one of the papers that one of our fellows had looked at many years ago. In which we saw that for colon cancer, there were 46,000 patients at that time point who had been enrolled in clinical trials of which only 600 had some version of peritoneal disease and there was no outcomes reported for these folks. So a very excluded population of patients, a very big population of patients, but excluded from clinical trials and excluded from a lot of treatments. And the problem then becomes those that do get enrolled on clinical
trials or those that have widespread disease or very measurable disease, they have big tumors, lumpy tumors. And so we look at these graphs and we’re very nihilistic. We’re like, ah, pertinent metastases. It’s, you know, not something that we would take care of and these patients should just go to Hospice. And I think palliative care is very important in the management of these patients, but but just being very nihilistic about this disease is not fair to these patients either.
And in fact, so much so that almost
five or six years ago, in fact,
when I started and when I had that graphic,
none of the surgical textbooks had a
chapter about peritoneal metastasis.
It's remarkable.
Now we do have many chapters because
of our constant advocacy work.
And then finally, you know,
when you think about sort of this
nihilism around peritoneal metastasis,
the question is why?
Why are these patients dying?
Are they dying of cancer, cataxia?
Do they die because these patients have
this sort of overwhelming interleukin
response that they can’t eat or drink and they kind of waste away?

Is this a catabolic phenomena like that or are they just dying because they have bowel obstructions?

It’s like if someone had renal failure and you don’t put them on dialysis and they die, you wouldn’t say, Oh my God, you know,

renal failure is such a horrible problem it it is a horrible problem because you don’t have treatment for it, but if someone has a bowel obstruction and you are unable to fix it.

You know is that is that truly
more the nature of the disease or

And so one of my colleagues at the University of Chicago, Ralph Wexselbaum, who’s one of the world leaders in in colorectal metastasis with liver tumors, actually coined the term oligo metastasis. And when you look at sort of colorectal and this is colorectal metastasis with liver tumors, there’s a completely differential expression of micro RNAs. There’s very different profiles and. And they published a lot of subsequent work looking at immune rich profiles.
which seem to do really well. These patients.

If you look at the X axis on the survival curve over here, it's 10 plus years, almost 15 years and you have about 40-40 to 60% of patients actually living that long when you have this sort of appropriate expression of your tumor. And this is one of those experiments where you know in this specific case they looked at micro RNA200C and you basically have vial RNA200C and you basically have vial type versus those that express it. And of course you can see an oligo
metastatic phenotype which is eligible for surgical therapies, radiation or ablation, ablative therapies versus those patients that have Poly metastatic phenotypes. And and similarly when you essentially reduce the expression of these micro RNAs you can actually see sort of some of these will have oligometastatic disease some of these will have polymetastatic disease. So clearly there is a differential phenotype of patients that can be cured. So not all stage 4 cancer is the same
NOTE Confidence: 0.939974802142857
00:11:43.735 --> 00:11:45.889 is is sort of where I I I would try to
NOTE Confidence: 0.925574476666666
00:11:45.948 --> 00:11:47.213 say these three slides or
NOTE Confidence: 0.925574476666666
00:11:47.213 --> 00:11:50.250 what what I wanted to convey.
NOTE Confidence: 0.925574476666666
00:11:50.250 --> 00:11:53.288 And so you know, how do we as surgeons
NOTE Confidence: 0.925574476666666
00:11:53.290 --> 00:11:55.117 You know, very often we would see
NOTE Confidence: 0.925574476666666
00:11:55.117 --> 00:11:56.450 patients with peritoneal metastasis.
NOTE Confidence: 0.925574476666666
00:11:56.450 --> 00:11:58.170 So you can see the livers down here,
NOTE Confidence: 0.925574476666666
00:11:58.170 --> 00:11:59.784 it’s a large amount of peritoneal
NOTE Confidence: 0.925574476666666
00:11:59.784 --> 00:12:01.569 metastasis is the phals form ligament.
NOTE Confidence: 0.925574476666666
00:12:01.570 --> 00:12:04.592 And very often surgeons would come
NOTE Confidence: 0.925574476666666
00:12:04.592 --> 00:12:06.769 we cannot do anything for these patients.
NOTE Confidence: 0.925574476666666
00:12:06.770 --> 00:12:08.390 But we’ve subsequently developed
NOTE Confidence: 0.925574476666666
00:12:08.390 --> 00:12:09.605 techniques called peritonectomies.
I tell patients it’s like peeling the wallpaper off the walls. So essentially you’re not destroying the walls, but you’re actually taking disease out. And so here you can sort of see what it looks like, it’s that Saran wrap which is underneath our instruments right here and the same patient you can actually strip or clean out that entire peritoneal layer by keeping an intact peritoneal SAC so that you can actually remove all of this in its entirety. So it is something that that is
interesting and surgically would become more more aggressive at it.
But right now this is a very, you know it is an aggressive approach.

You know you can see this is a big laparotomy incision.
The head of the patient is on one side, the feeder on the other.

And after we remove all this cancer, we put heated intrapartinial chemotherapy.
The the concept is that you know you have application of chemotherapy at high doses which has low toxicity.
to systemic absorption is very low, you can actually enhance the penetration of the drug. You know these tumors are very hypovascular, so you can kind of enhance the vascularity during that period of the application. But again it’s, it’s a little bit also controversial because you know how does one application of chemotherapy work so effectively versus multiple applications that we do in the systemic setting. And clearly you know now we do these laparoscopically as well in selected
patients when we find disease early, so we can deliver heated chemotherapy that way. And then also now what is very hot in Europe and Asia is intrapertinal aerosolized chemotherapy where you can actually distribute the drug a lot better across the entire peritoneal cavity. This is called pipec and over 10,000 procedures have already been done in the world for these technologies. And as you would imagine a lot of these patients require very close management as a team.
the team that consists of physicians.
Which consists of nurses and dietitians

And only when you do

that you're able to achieve you know,

good outcomes.

we were before I left the

University of Chicago,

we did about 180 procedures a year.

We were able to reduce the length of stay

for patients from 10 days to six days,

the benchmark programs being

MD Anderson and Wake Forest and

readmission rates of 8%.

So it took a lot of effort for

us to bring this program together.
For patients that had peritoneal metastases, but the biggest question is well, is it helping these patients, are they living longer? Is it worthwhile to do these aggressive approaches for these folks and this is what happens when patients get selected patients with good performance status get systemic chemotherapy, that’s the reference survival data right here.

And then of course those that had cytoreductive surgery, this was our own data for
00:14:53.016 --> 00:14:54.200 How these patients did.
NOTE Confidence: 0.943723035714286

00:14:54.200 --> 00:14:56.195 Only about 20% of our high grade
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00:14:56.195 --> 00:14:58.039 patients live 10 years or longer.
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00:14:58.040 --> 00:14:59.632 So if you look and remember the graph
NOTE Confidence: 0.943723035714286

00:14:59.632 --> 00:15:01.386 that I showed earlier for those that
NOTE Confidence: 0.943723035714286

00:15:01.386 --> 00:15:04.599 enrolled in NCT and clinical trials
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00:15:04.600 --> 00:15:05.980 that were good performance status,
NOTE Confidence: 0.943723035714286

00:15:05.980 --> 00:15:08.440 patients got systemic chemotherapy.
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00:15:08.440 --> 00:15:10.099 No one lived more than five years.
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00:15:10.099 --> 00:15:11.440 So you do have the select population
NOTE Confidence: 0.943723035714286

00:15:11.440 --> 00:15:13.240 But the question is where do we go from here?
NOTE Confidence: 0.943723035714286

00:15:13.240 --> 00:15:14.800 How do we make this better?
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00:15:14.800 --> 00:15:17.144 And this is really where I think it’s
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00:15:17.144 --> 00:15:19.400 important for all of us to think about it.
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00:15:19.400 --> 00:15:20.340 So the first question we
want to ask ourselves is, can you actually prevent peritoneal metastasis? And I’ll show you some science behind this, but something that is very interesting is that a recent trial that was just looking at patients that had T4 colon cancers, nothing has spread outside and. On that patients actually have better local regional control. If you apply intraperitoneal chemotherapy at the time of a primary cancer resection without peritoneal metastasis, can you actually,
can you actually reduce that?

And so if you think about it

And this is something I will, I will tell you is is very interesting science.

And this is science that was done by one of my colleagues at the University of Chicago.

Where we’re thinking about the intestinal microbiome, I think many of you might have heard about the important role of the microbiome and thinking about carcinogenesis as well as development of metastases. And clearly in a Peri operative event.
we change the microbiome of the intestines. And so the hypothesis for their experiments were to look at what happened if you took a Western diet. So essentially the experiments were in in mice you basically. Resected the colon, put colon cancer cells inside it, and then you gave them a collagenolytic bacteria called ephycallus. And then you gave them a collagenolytic bacteria called ephycallus. With the hypothesis that collagenolytic bacteria cause increase in astomatic leaks.
So this is their work.

This has been their life's work on this and it's remarkable and there's lots of experiment that support that it causes this.

But what was interesting to me.

Is when you actually look at this, all the tumors that developed were on the serosal surface and not on the mucosal surface.

So all of them came on the serosal surface.
A lot of these mice ended up dying of peritoneal metastasis. It’s a very interesting credence to the theory that perhaps there may be a microbial alteration that is occurring in these primary cancer resections that is leading to these patients getting peritoneal metastases. And what is very funny is that one of our colleagues in Belgium said maybe the reason mitomycin which is our intraperitoneal chemotherapy works is that it is also an antibiotic.
provoking way of thinking about.

Where the microbiome lies as we think about why patients get hurt in metastasis,

but if we can find these tumors and we can actually detect them early and we can treat them,

these patients beat the survival curves. So this is the survival of patients that if they were found early and had surgery,

you can look at the X axis is five years and you can see that 90% of these patients are alive at five years.

So really a,

can you prevent them and B,

can you find them if they’re very early and then treat them.
That is sort of really where we need to move the needle and that’s really where I would love for us to think about it, about it together. And so the problem is conventional cross-sectional imaging. So this is a CT scan on a coronal view of a patient and on a cross-sectional imaging, the peritoneum is incredibly difficult to image. So the imaging of the peritoneum, if you can see my cursor, which you cannot, is actually this line that kind of goes along the colon. It’s this sort of little little fun time.
stuff here. This stuff right there,
NOTE Confidence: 0.94696245333333
that’s the first name right there.
NOTE Confidence: 0.939212499655173
And so it is, it is very difficult for
NOTE Confidence: 0.939212499655173
us to believe that our radiologists
NOTE Confidence: 0.939212499655173
are going to be able to tell us that
NOTE Confidence: 0.939212499655173
a patient has peritoneal metastasis.
NOTE Confidence: 0.939212499655173
It is just not feasible.
NOTE Confidence: 0.939212499655173
You can certainly tell if someone
NOTE Confidence: 0.939212499655173
has liver metastasis or not,
NOTE Confidence: 0.939212499655173
but it’s very difficult to tell
NOTE Confidence: 0.939212499655173
if they have peritoneal meds.
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And so we’ve played with this
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along with many,
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many other groups and there’s a lot of
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radiomics work that folks have done.
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We’ve done our own radiomics work.
We did some work with our physics group at the University of Chicago and try to kind of pick up better ways of looking at the pertinum. You can look at panel B, you can sort of see how you can actually enhance the pertinum better by kind of playing around with contrast agents and how do you give it later? How do you give it earlier and how does that kind of make a difference? I think the other thing that we've very been very interested in is study of circulating DNA,
whether it’s cell free or whether it’s circulating tumor DNA. And clearly we know as surgeons that it’s very prognostic. What do we do with that information is still something we’re all trying to figure out. But we know that if they’re, if they don’t have cell free DNA prior to surgery and you operate or at least vary in cell free DNA before surgery you operate and they stay negative. These patients will do really well, whether it’s GI cancers of different types or other types of cancers. And so this is some of our work.
that just got published as well and was one of the plenary sessions. Some of you have heard this before. But really what we did was we took patients who had peritoneum metastases. We did surgery for these folks and then we studied them and followed them at CTDNA. We said can we actually figure out a better way of identifying these tumors early and the answer was yes, CTDNA did work for us. This is a small sample size with numerous assessments. It’s not 100% sensitive.
It was only about 90% sensitive in this cohort, and it did have a false negative rate. Patients who did have undetectable CTDNA, 1/5 of them still had peritoneal metastases. In fact, if you look at cohorts of different technologies, many times you have florid peritoneal disease and they shed almost no CTDNA. One of our research fellows was run in the back has just submitted an abstract where if you have a single solitary liver metastasis your CTDNA is super high. But if you have a full abdomen full of peritoneal metastases,
you have almost no CTDNA in the range of like point some MTM per ML.

So it’s a remarkable phenomenon that the burden of tumors this is almost the same or even many fold more, but it doesn’t shed it. It gives credence to the belief that maybe local regional treatments like surgery, intravertinal chemotherapy may have a role in these sort of metastatic settings and then as expected if they shed DNA they do worse. If they don’t shed DNA, they do a lot better and that’s sort of what we saw in this.
And the biggest question was we saw these patients you know three months before they showed up on scans and you know ceas and things like that. But really the bigger question is what are we going to do with that information and how do we make it practical for our patients. And so you know some of our research has been focused a lot on looking at epigenetic modifications and why this is important is because right now we need a large amount of DNA to actually do CT DNA, to do other types of cfDNA.
can we actually extract DNA at very low levels without the bisulphite conversion so that it doesn’t destroy a lot of the DNA in the blood and then look at alterations in a cheap sort of reproducible way? And so this is where we work with one of our chemists, Schwan hey, who actually came and gave chemistry grand rounds not long ago at Yale. And a phenomenal colleague and collaborator, you know basically looking at HMC and now we’re looking at 5 HMC modifications. So we have different sorts of
modification profiles and and his lab has already shown and this is I think published in cellular science. But looking at sort of the five HMC distributions of patients and you can identify patients who have cancer versus controls, adenomas versus controls and then what we found was peritoneal disease versus no peritoneal disease. We also had understanding of the mechanistic underpinnings of peritoneal metastasis and you know I’ve identified some epithelial meas and camel.
00:23:06.650 --> 00:23:07.890 transition markers that potentially
00:23:07.890 --> 00:23:10.786 could be part of our signature to
00:23:10.786 --> 00:23:13.478 identify peritoneal disease better.
00:23:13.480 --> 00:23:14.956 So switching gears a little bit,
00:23:14.960 --> 00:23:17.678 you know So what I what I hope I’ve
00:23:17.678 --> 00:23:19.786 emphasized in this first few minutes of
00:23:19.786 --> 00:23:22.459 my talk is that peritoneal metastases.
00:23:22.460 --> 00:23:24.458 There may be population of patients that
00:23:24.460 --> 00:23:26.497 are treatable with local regional therapies.
00:23:26.497 --> 00:23:28.658 We struggle to figure out how
00:23:28.660 --> 00:23:30.508 to identify these patients,
00:23:30.508 --> 00:23:31.740 whether it’s with cross-sectional imaging,
00:23:31.740 --> 00:23:33.700 radio omics,
00:23:33.700 --> 00:23:34.268 that type of work or whether
it’s with cell free DNA work,

although there’s promising avenues in both of these.

So the question comes to how can you actually think about treating these patients?

Are there things we can do differently?

In clinic, we often see patients coming and saying I stopped having sugar because I was told I have cancer, and I’ve told sugar feeds these cancers and really what happens to these tumors. We believe that these tumors are hypoxic.

We believe that the peritoneum has very little vasculature as compared to say the liver and other sort of solid organs.
like the lungs and we all know that.

You know tumors as they
develop metastatic potential,

they rely more on anaerobic pathways,

but they also still have location

specific metabolic needs specifically

around oxidated phosphorylation.

And so the question is,

is where are these tumors

getting their fuel from?

So again can you interrupt this field?

And so we did a couple of trials

with one of my colleagues,

Ernst Langel over there where

gave patients sort of tracer
labeled glucose and kind of studied these tumors and and clearly they go along more anaerobic pathways. You see a lot more lactate in these tumors and they kind of use different metabolic substrates as they’re kind of getting it. But what was very interesting is the omentum, which is the commonest site of peritoneum metastases. And we don’t know why it does have a very rich source of fuel with which is adipocytes. And and in these experiments what basically Ernst Group showed was that when you actually control
for Fab BP4 which is associated integrally with adipocytes, you can actually reduce the amount of in vivo metastasis in mice and so essentially it is somehow. You know, lending critics to the theory that the adipocytes that are in the momentum are providing fuel as opposed to a lot of the vasculature which provides fuel to these pertinent metastases. Very interesting preliminary work. It’s again not meant for you know like inpatient care right away,
but I think very interesting for us to think about how do we take care of these patients and perhaps how do we think about alteration of adipocytes. And the other thing we’ve been very interested in is how do we actually enhance the effect of intraperitoneal chemotherapy, how do we leverage this to enhance the care of these patients. So these are patient panels where we had patients with high grade unresectable tumors, where we did multiple applications of intraperitoneal chemotherapy only, no surgery and we actually almost developed complete pathological...
responses as you can see in panel C for these patients that had very high grade disease that we would not have routinely offered surgery for. And they lived exactly the same as those that we did open big and I don’t have that data here, but they all had alterations in their P, DL1 expression, their C, and some PS. have now a clinical trial for adding...
an intravertinal chemotherapy plus immunotherapy for these patients that are otherwise cold tumors. These are incredibly cold tumors. If you look at the TCGA Atlas, a lot of these GI tumors actually have a lot of you know sort of hot immune signatures. But when you actually go to giving these folks checkpoint inhibition or do any sort of conventional immunotherapy, they don’t respond as well unless they’re MSI high or they have specific characteristics. And so with intrapartial chemotherapy we believe that you can actually change some of the immune profile of these tumors.
And so I think in the last, you know maybe 5 or 10 minutes of this of my talk. You know I just wanted to tell you that there are numerous unanswered questions in the management of peritoneal metastasis. Numerous I will tell you that we don’t even know the basics of the immune environment of the peritoneum. Numerous I will tell you that we don’t even know the basics of the immune environment of the peritoneum. It’s fascinating. I was talking to Steve Rosenberg and I asked him, I said do you understand the immune environment of the peritoneum and the bottom line is for some
00:27:35.994 --> 00:27:37.268 you know many of the labs many,
NOTE Confidence: 0.931922738888889
00:27:37.270 --> 00:27:39.355 many animal models look at
NOTE Confidence: 0.931922738888889
00:27:39.355 --> 00:27:40.189 intrapertinal tumors.
NOTE Confidence: 0.931922738888889
00:27:40.190 --> 00:27:42.325 But we actually don’t understand what the
NOTE Confidence: 0.931922738888889
00:27:42.325 --> 00:27:44.149 native immune environment of the pertinum is.
NOTE Confidence: 0.931922738888889
00:27:44.150 --> 00:27:45.625 How is T cell trafficking
NOTE Confidence: 0.931922738888889
00:27:45.625 --> 00:27:46.510 happening over there?
NOTE Confidence: 0.931922738888889
00:27:46.510 --> 00:27:48.071 What is the repertoire of T cells
NOTE Confidence: 0.931922738888889
00:27:48.071 --> 00:27:49.508 that are present in the pertinum.
NOTE Confidence: 0.931922738888889
00:27:49.510 --> 00:27:50.834 We understand what happens
NOTE Confidence: 0.931922738888889
00:27:50.834 --> 00:27:51.827 when there's peritonitis.
NOTE Confidence: 0.931922738888889
00:27:51.830 --> 00:27:53.405 We certainly know that when
NOTE Confidence: 0.931922738888889
00:27:53.405 --> 00:27:54.350 someone has inflammation,
NOTE Confidence: 0.931922738888889
00:27:54.350 --> 00:27:56.789 what happens to these tumors and how do they,
NOTE Confidence: 0.931922738888889
00:27:56.790 --> 00:27:58.710 what happens to the the diseases
NOTE Confidence: 0.931922738888889
00:27:58.710 --> 00:27:59.990 and the inflammatory processes.
But we don’t actually understand what happens to these clinically. How we see this is many times our patients are dying because of the inflammatory response. They die of bowel obstructions because the tumors create the significant inflammatory response, it causes mesenteric fibrosis and then we’re unable to fix these bowel obstructions that these patients have. And so we don’t understand this. The other work that is very interesting is that we all know that the vent beta ketenin pathways are
activated in a lot of these GI tumors
NOTE Confidence: 0.931922793888889
that cause peritoneum metastasis.
NOTE Confidence: 0.931922793888889
But what we have also seen is
NOTE Confidence: 0.931922793888889
the conventional bad actors,
NOTE Confidence: 0.931922793888889
the B RAF mutant tumors.
NOTE Confidence: 0.931922793888889
They don’t do as poorly when
NOTE Confidence: 0.931922793888889
they have peritoneal metastasis.
NOTE Confidence: 0.931922793888889
They actually do almost exactly the same.
NOTE Confidence: 0.931922793888889
And indeed it’s the big three CA
NOTE Confidence: 0.931922793888889
pathways that are mutated that
NOTE Confidence: 0.931922793888889
seem to predict differently.
NOTE Confidence: 0.931922793888889
So they do differently based on sort
NOTE Confidence: 0.931922793888889
of what they’re signaling pathways.
NOTE Confidence: 0.931922793888889
And we don’t understand that.
NOTE Confidence: 0.931922793888889
We don’t know why that is the case.
NOTE Confidence: 0.931922793888889
And then finally,
there's a lot of science about pharmacokinetics of drugs and novel drug delivery. We know that if you give someone systemic chemotherapy by the time it crosses the plasma peritoneal barrier. The concentration of the drug depending on the molecular size of it is one by two to the 10th, so 1 by 1000 and 24th of the serum concentration of this chemotherapeutic and that is a remarkably low dose of systemic chemotherapy when it comes to the peritoneum. The question is how do you...
How do you actually change that such that your drug substrate substrates are able to actually enter the peritoneum? And how do you think about the pharmacokinetics? I'm just, I just have two like sort of quick slides for for folks to look at. And this is the work that was actually done by one of our medical students. Most of it has been done by either our lab or one of our collaborator labs. And it's all been driven by medical students, residents,
undergraduate research students, fellows. And so I, we truly have been very hungry for young, you know smart minds to come work with us to help figure out how do we actually make a difference in this. And this is just the work looking at the number of pathways that are altered for patient with pertinum metastases. And you know of course the APC pathways are always affected in a lot of these. GI tumors here as about half of the time. But the big three kind is which we thought was the most important pathways in particular metastasis only about
00:30:12.299 --> 00:30:15.002 17% and of course mad for 11% and
NOTE Confidence: 0.922453161052632
00:30:15.002 --> 00:30:17.234 then this sort of you know and again
NOTE Confidence: 0.922453161052632
00:30:17.234 --> 00:30:18.610 done by one of our medical students.
NOTE Confidence: 0.922453161052632
00:30:18.610 --> 00:30:18.970 So,
NOTE Confidence: 0.922453161052632
00:30:18.970 --> 00:30:21.286 so remarkable sort of work and then
NOTE Confidence: 0.922453161052632
00:30:21.286 --> 00:30:22.834 this is something where we’ve been
NOTE Confidence: 0.922453161052632
00:30:22.834 --> 00:30:25.192 looking at microparticles and how do you
NOTE Confidence: 0.922453161052632
00:30:25.192 --> 00:30:26.620 actually deliver microparticle based.
NOTE Confidence: 0.922453161052632
00:30:26.620 --> 00:30:27.172 Packlet axle,
NOTE Confidence: 0.922453161052632
00:30:27.172 --> 00:30:29.380 2 tumors and what we discovered is that
NOTE Confidence: 0.922453161052632
00:30:29.435 --> 00:30:31.780 these microparticles are just bound by mucin.
NOTE Confidence: 0.922453161052632
00:30:31.780 --> 00:30:33.362 So mucin just kind of binds it
NOTE Confidence: 0.922453161052632
00:30:33.362 --> 00:30:34.805 and doesn’t let it distribute
NOTE Confidence: 0.922453161052632
00:30:34.805 --> 00:30:36.217 within the peritoneal cavity.
NOTE Confidence: 0.922453161052632
00:30:36.220 --> 00:30:37.708 And so this is just sort of some
NOTE Confidence: 0.922453161052632
00:30:37.708 --> 00:30:39.422 of the other work that’s coming out
right now when we’ve been working with one of our pharmacologists to try to figure this out and really finding that, you know, it really binds our nanoparticles and microparticles that we’re introducing in the peritoneal cavity. So just kind of a very tough space. But that exactly that is why it makes it exciting. That’s why we’re Yale because, you know, we don’t address simple problems. We want to take on the tough problems.
all of you smart folks here is, is so important and exciting to me. And so my pitch for all of you would be that it's a poorly studied field, but it has a large impact. There's a huge population of patients that would benefit tremendously. From improvements in the management of peritoneal metastasis. So, I welcome all of you if you're interested. There's lots of tissue. We do laparoscopies for these patients. We take out tons of tissue. Sometimes my tissue specimens go across the alphabet.
which means I have more than 26 specimens per case. So lots of tissue to be drawn. Most of these patients are very generous. It is not infrequently once a month or once twice a month I get an e-mail of someone who wants to donate their body to science research. And that is probably the most generous gift that any human being can ever make. But we don’t know what to do with that. Like what do we do with that. We don’t even have a mechanism of studying that or making use of it. It’s a nice window of
opportunities environment.

We're able to give chemotherapeutics.

We're able to give Immunotherapeutics to patients. We do laparoscopies, we get biopsies, we go do surgery. 2 weeks later, we can actually show you and get you tissue for how these patients will do afterwards as well.

I think these patients have a significantly tough time, not only with the disease, the lack of knowledge of the disease. 90% of patients who would come to my clinic were told they were going to live less than three months, 90% we actually
we actually did a survey and we asked people in our waiting room and they had been told by some healthcare provider who did this. We did a lot of education around this. We have lots of processes of working together. Jen Capital is here and we were just chatting about this. But how do we cointegrate palliative care into our clinics so that we make sure that we're, we're taking care of the human being as a whole and not just you know pertinent metastases or not just GI cancer,
but we’re taking care of our patients and appropriately transitioning when we’re not able to provide them with therapeutic options. And how do we build clinical trials in this space you know how do you advocate for pharma companies. To get allow these patients to get onto clinical trials, because right now we cannot put these patients on clinical trials. Many times you have ascites that’s not enough. Or if you have tumors which are very small, don’t even fit the 1 centimeter category, you can’t put them on a clinical trial.
So there's a big initiative at the Coke Institute at MIT where we're trying to get together to try to figure out how do we, how do we fix this. But I think it's a great space to build a career.

That is what I will tell you when I started as a surgical oncologist. You know, every surgical oncologist, for those of you that may not know what we do, we want to do the big liver pancreas operations. That is sort of the sexy thing.
for us to want to do.

And that's what I wanted to do.

I wanted to do robotic whipples.

That's what I went and trained and I became an expert in that.

And I said I published the first series of how to do robotic whipples and I said this is what I'm going to make my career on.

I got a job offer from Milwaukee, even though it paid less, just because I had the right people to work with.
I had good mentors and that was the best decision of my life. But they said, oh, you know, you can do sort of liver and pancreas, but why don’t you do this stuff? And I said, oh, OK and I started doing it. And I love my patient population and I love what I did. It was a tough problem. No one else wanted to do it. And so I got to write the book chapters, I got to write be at the podiums, I got to be coming and doing all of this stuff. And here look at me, I’m.
I'm division chief of surgical oncology, one of the best divisions in the world. So it is a remarkable space and not much has changed. Yes, some has changed, but I think it's a great opportunity for those of you that are excited to build your careers on this because there's not those many people that want to do this stuff or can do this stuff really well. So I would say we were looking for collaborations, lots of partnerships and feel free to reach out.

I do have to acknowledge this is
00:34:54.574 --> 00:34:55.990 obviously not a comprehensive group,
00:34:55.990 --> 00:34:57.278 but this is some of my group
00:34:57.278 --> 00:34:58.150 that we’ve worked really,
00:34:58.150 --> 00:34:59.940 really closely on for understanding
00:34:59.940 --> 00:35:02.110 a lot of our chemistry work.
00:35:02.110 --> 00:35:05.450 A lot of our fellows and residents that I,
00:35:05.450 --> 00:35:07.150 I have not acknowledged,
00:35:07.150 --> 00:35:08.941 but I have some of their work in the
00:35:08.941 --> 00:35:10.763 in the slides that have really been
00:35:10.763 --> 00:35:12.858 very helpful and a lot of funding that
00:35:12.858 --> 00:35:14.700 we’ve had over the years that have
00:35:14.700 --> 00:35:16.175 that have supported our research.
00:35:16.180 --> 00:35:17.174 So with that I’m going to stop.
00:35:17.180 --> 00:35:19.180 I know it’s a little early but but
00:35:19.180 --> 00:35:20.950 I’d welcome any questions or comments
and love a good discussion on
and of course this is this is my cell phone and e-mail.
So thank you again for your attention today.
Go ahead
Laura. So I think this talk together the context of like a legal mess that you need for.
And I'm hoping you could weigh in on your perspective on the difference of what your new goals are when
00:36:16.210 --> 00:36:17.810 you’re working in this space,
00:36:17.810 --> 00:36:20.730 whether you’re considering it,
00:36:20.730 --> 00:36:24.982 no matter whether you’re considering
00:36:24.982 --> 00:36:26.650 it like a rapid process or if
00:36:26.650 --> 00:36:28.050 that matters and try to discuss
00:36:28.760 --> 00:36:29.768 Yeah. No, great question.
00:36:29.768 --> 00:36:32.092 And I think that one of
00:36:32.092 --> 00:36:33.604 the things that we’ve tried to
00:36:33.604 --> 00:36:35.480 do quite deliberately is we’ve,
00:36:35.480 --> 00:36:37.655 we’ve separated the term cycle
00:36:37.655 --> 00:36:39.395 reduction from debulking.
00:36:39.400 --> 00:36:41.656 So I think when we use the word
00:36:41.656 --> 00:36:43.980 we’re talking about
00:36:43.080 --> 00:36:44.680 enhancing quality of life.
So those are not very frequent settings, but we would do debulking procedures if patients have large amounts of mucinous societies or large amount of mucin that is debilitating or large ovarian metastasis that is making it difficult. Those are the bulking but non-curative intent procedures. For the curative intent procedures, we call them site reduction and we have very specific goals of what we want to achieve, which is a CC0 site reduction, which means there’s no visible cancer with oncological principles of surgery. So no longer are we satisfied with,
we just go pluck a little something out and feel like we’ve done a great job.

We have to be oncologically precise in the way we’re doing our surgical techniques, just like we are when we’re doing liver resections, pancreas resections or things like that. The drawback is we can’t image it. So we don’t know what a good, good or bad job we’ve done. And so one of the big things we’ve been doing is making sure our laparoscopy pictures, our surgical pictures are actually in the chart and we can review,
00:37:39.040 --> 00:37:40.594 review it with the patients because many
NOTE Confidence: 0.916983122083334
00:37:40.594 --> 00:37:42.320 times they don’t even know what’s going on,
NOTE Confidence: 0.916983122083334
00:37:42.320 --> 00:37:43.679 right.
NOTE Confidence: 0.916983122083334
00:37:42.471 --> 00:37:43.679 They look at the scan and they’re like,
NOTE Confidence: 0.916983122083334
00:37:43.680 --> 00:37:45.536 oh, the doctor said I don’t have much
NOTE Confidence: 0.916983122083334
00:37:45.536 --> 00:37:47.284 cancer and you look inside and
NOTE Confidence: 0.916983122083334
00:37:47.284 --> 00:37:48.516 there’s just cancer everywhere.
NOTE Confidence: 0.916983122083334
00:37:48.520 --> 00:37:51.832 And so, so we’re very specific in our intent.
NOTE Confidence: 0.916983122083334
00:37:51.840 --> 00:37:52.984 I think, you know,
NOTE Confidence: 0.916983122083334
00:37:52.984 --> 00:37:54.738 usually I try to have three
NOTE Confidence: 0.916983122083334
00:37:54.767 --> 00:37:56.757 visits with every patient prior.
NOTE Confidence: 0.916983122083334
00:37:56.760 --> 00:37:59.576 And in my ideal world with our palliative
NOTE Confidence: 0.916983122083334
00:37:59.576 --> 00:38:01.639 care physicians for the three visits,
NOTE Confidence: 0.916983122083334
00:38:01.640 --> 00:38:03.075 but really the first visit is where
NOTE Confidence: 0.916983122083334
00:38:03.075 --> 00:38:04.738 I kind of give people hope because
most of them have already been told, you know, three months they're going to live and die and whatever.

And I tell them, hey, listen, this may not be quite the same. Let's assess it and evaluate it. The second visit is where we really just go through the numbers and again, you know that very nice essay by the evolutionary biologist of like how median is not the mean and, it’s not the message and. And you know,
It's very hard for patients to wrap their heads around it, but I do think it's important for them or their caregivers to at least understand what the reasonable expectations are.

What is our survival data that we have? What is sort of best case scenario, what is worst case scenario? And are we using the hitchhiker model, like are we trying to keep people alive like a diabetes chronic disease type model and saying, hey, we'll look for this next disease site or are
we saying we’re going to
And that’s where we really have a lot of conversations about goal matching and how are we doing the right thing.
And then the third visit is just much more specific around the surgical procedure and what does that involve and everything else.
So, so you know we’ve tried to take a very deliberate approach,
but I will tell you that having another physician or another team member in this conversation that may not be a surgeon, you know, very often obviously our
00:39:12.836 --> 00:39:14.760 medical oncologist we were Co, you know,
NOTE Confidence: 0.914861194285714
00:39:14.760 --> 00:39:16.460 seeing patients or palliative care
NOTE Confidence: 0.914861194285714
00:39:16.460 --> 00:39:18.620 physicians was really helpful for patients.
NOTE Confidence: 0.914861194285714
00:39:18.620 --> 00:39:20.028 Because, you know, I'm an optimist and I
NOTE Confidence: 0.914861194285714
00:39:20.028 --> 00:39:21.346 can sell things different ways, right.
NOTE Confidence: 0.914861194285714
00:39:21.346 --> 00:39:22.248 I mean I could say, oh,
NOTE Confidence: 0.914861194285714
00:39:22.248 --> 00:39:23.856 you know, surgery is no problem.
NOTE Confidence: 0.914861194285714
00:39:23.860 --> 00:39:24.580 It’s a big no, it’ll be fine versus,
NOTE Confidence: 0.914861194285714
00:39:24.580 --> 00:39:27.206 you know, Oh my God,
NOTE Confidence: 0.914861194285714
00:39:27.206 --> 00:39:29.124 you're going to do poorly.
NOTE Confidence: 0.914861194285714
00:39:29.124 --> 00:39:29.780 it’s a tough surgery and you’re
NOTE Confidence: 0.914861194285714
00:39:29.780 --> 00:39:30.467 going to do poorly.
NOTE Confidence: 0.914861194285714
00:39:30.467 --> 00:39:32.457 we have a lot of power in how
NOTE Confidence: 0.914861194285714
00:39:32.457 --> 00:39:34.102 we can actually navigate this
NOTE Confidence: 0.914861194285714
00:39:34.102 --> 00:39:35.783 conversation and having a sounding
00:39:35.783 --> 00:39:37.890 board for the patients to talk to

00:39:37.890 --> 00:39:41.340 someone who is perhaps not quite, you know,

00:39:41.340 --> 00:39:44.264 as narrow minded or or as focused I should say.

00:39:44.264 --> 00:39:45.350 Has helped I think generally our patients make the right decisions and I think for all of us to also internalize the fact that you know to make sure that we’re not pushing therapies on our patients and especially when we’re not seeing a good sort of outcome on the end.

00:40:01.390 --> 00:40:03.110 So I think it’s a very complex thing.
face it in our clinics every day and what I’m saying is probably not unique,
Is being deliberate about it and also it has helped our team.
You know, I will tell you,
we go through cycles of despair even as,
you know, physical teams like our,
our nurses, physicians,
everyone who takes care of these patients.
Because you see people that look like you could be your friends,
neighbors, colleagues who are dying a very miserable death.
And you know,
we took care of all these patients
all the way through Hospice.

So it is, it is a very difficult thing to kind of be part of the process. And so I think it rejuvenates to have other physicians, providers and then of course having a clinic that’s balanced because you have 20 people that are doing great and you have you know maybe three or four that are not.

So we’re so thrilled you’re here. I think you’ve heard me say that many times and I’ll repeat it again.
So I’m going to build on the conversation that you were more we’re just having and as curious. Just on into patients that come to desiring this therapy aren’t a yearly candidates that or maybe it wants to decide not to pursue the decide on productive therapy. And then the other related to that is he talked about the recovery from that surgery. So what does it look like? Yeah, so I think what when we’ve looked at our own data I would say about 67% of our patients had. You know, at least a diagnostic laparoscopy and about 50% of our
patients who came through our doors ended up having cytoreductive surgery. So 50% didn’t have it.

So as you can tell, we are selective, but we track our whole cohort.

So we’re not just saying, oh, we’re going to just look at those that we’ve done surgery and say this is how well we’re doing it. The second comment is it, really dependent on the surgery itself. It’s a whole gamut of things.

When we do a laparoscopic hypec, they go home the same day. I tell them they can do their normal
physical activities like the next week.

So that’s what when we just do a laparoscopic one,

when we do these big monster open side reductions, hypex 812,

14 hour cases right now our median hospital stays about 5 to 6 days.

But I tell them they feel about 80% of normal in six weeks and they feel 110% of normal at three months because now the cancer is better,

But this is all generally sort of what things are.
00:42:20.056 --> 00:42:22.300 during discussion of surgery is not so much mortality because our mortality rates, as you saw, are very low. It’s more about loss of autonomy and functional independence. So you know there’s an 8% risk of having failure to thrive. You know then you are on TPN, you’re getting drains, you have this and that and I think that is the most stressful part of these. But we’ve tried to integrate sort of quality of life initiatives,
you know fertility management,

you know young patient care,

obviously palliative care and advanced
direct advanced care planning.

So you know the goal is to have a more comprehensive way that patients get the most information.

I know that this is a slowly evolving deal with what we discussed, but has it been evaluated from a racial, ethnic standpoint as far as incidents of care communities along with outcomes?

So I mean, I think we have, you know, obviously our own cohorts and our own data that we’ve looked at.
And in Chicago about 17% of our patients were African American and I think about, you know, maybe another 15% were other ethnicities and everyone else was white. I think the we found that our African American patients were less likely to do advanced care planning, they were less likely to look in clinical trials. They were usually presented with a higher PCI score, with a higher pertinal index, but actually recovered remarkably the same from cytoreductive surgery procedures. In fact you know at some level I would
say that at least in Chicago

or African American population had

better social structures than some of

our white populations of patients.

And I think it’s a very selective

cohort because I think the the

African American patients who were

didn’t have the means or lived in

food deserts or things like that,

they probably never made it to our clinics.

So I think you know I’m very

cognizant of that.

But those that did make it to our clinics

actually had remarkable social support,

so much less rates of post

operative depression or you know
so they did pretty well. From a survival standpoint, I don’t know. Vrun probably left, but I don’t think we’ve seen a significant difference. But I don’t think our cohort is big enough to make that conclusive. There are a couple of questions in the Q&A and the chat. Ask for Nas feeding. So Nick, Nick says. Is there any consistency in localization in terms of where the metastasis form in the peritonema momentum?
I’m wondering if it’s random or if it’s in proximity to lymphoid tissues.

Nick, you know this is a phenomenal question and I will tell you that in our minds as surgeons there is very remarkable consistency like we see it on the right diaphragm. We think it’s because there’s Milky spots on the diaphragm, big channels. We always see it in the momentum. So those are very common sites. Mechanistically, we see it by the ligament of triads as a very common site. And then in the pelvic peritoneum,
especially on the left side, in fact, you'll see many of these peritoneal patients will have bowel obstructions and they obstructed the pelvis as the sigmoid colon is turning down. And in those cases, stents don’t work very well. And so that’s usually the thing. I don’t think it’s particularly close to lymphoid tissues, but I think that’s where hopefully we’ll send you some specimens and you can help us figure it out. And then I think Guillermo, Hi Guillermo it’s good to see you
as one of our colleagues from Mexico who says what are your thoughts on the debate for drug combinations on hyper protocols. I think we just need to do better. I think you know mitomycin is like a 60 year old drug and you know we've just got to figure out better ways of doing it. So people are looking at intrapartinal immunotherapy now on different versions of cytotoxics. Do you ever analyzed CTD and A? We don’t but we there are
other groups that have looked at it and certainly it is more sensitive than serum CT DNA. But on the flip side it’s logistically impractical. So you know you have to leave a catheter in there and measure it and stuff. So I think that’s the headache with that. Great, ohh, very good. Thank you so much. Thank you all for your attention.