So I'm Roy Herbst, Deputy Director here at the Cancer Center, and it's really my honor to introduce the Cal Brazy Lecture. And this year you'll meet Doctor Pasiani, who will be introduced by our lung program, scientific leader Katie Poletti and clinical leader Sarah Goldberg. But first, I just want to say a word about Paul. Cal Brazy is often referred to as the father of oncology and its influence...
here at Yale Cancer Center remains a former faculty member at Yale School of Medicine who was internationally recognized as an authority on the pharmacology of anti cancer agents. Doctor Calabrazzi serves as director of the Yale Cancer Center's Advisory Board until 2003 and we honor him with a conference room where his picture hangs and I bet almost everyone here has visited. You can see here’s the conference room shown on the slide with a beautiful portrait of Paul and all the lecturers, the 13 who have given this lecture over the last 14 or 15 years have shown and
Doctor Yanni’s plaque is already there and you can see the outside of the room. So if you haven’t been to the room, we were just there and it was just wonderful to be with the Cal Brazy family and I welcome them all here today and to take some photos.

This is a list of the lecturers. This is a very important lecture. You know, Paul was you know who who here has AK12 award? Do we have any of our K12 awardees here? They’ll be.

Yep, Yep so. So we have.
So K12 is the Calabresi award.

Paul was all about mentorship, teaching, taking care of the patient. He was both a scientist and a clinician.

The true what we used to call the three legged stool.

So we try to invite people to these lectures and you can see the list of lecturers. And the very first one was Eddie Chu, also a mentee of Paul.

And here are just some photos over the years. And last year we had Steven Rosenberg.

It's very special lectureship for me because I actually met Paul 44 years ago.

And how did I meet Paul? I have a picture,
I can only find 2 pictures on the left, that’s Paul behind his wife Seal. And that’s me at my friend Peter Calabresi’s wedding, the only picture Janice could find for me. But Paul was mentoring me and how to walk and stand stand up straight. And then on the right Paul took this picture. There’s another picture with Paul but I couldn’t find it. But that’s Peter and I just a few years ago probably around 1983. You can see I’m drinking a tab but, but but Paul was a mentor to me as to so many.
That's always so special for me to have this lecture. And here we have Paul's brother Guido in the audience. His wife Ann was with us last night. His sons Peter and Steven. His daughter Janice Mimi, who is Steven's wife. So it's just wonderful to have the Calabria family here. But now to introduce our guest of the day, our speaker, I'm going to invite Sarah Goldberg and Katie Paletti to introduce Doctor Yanni. Good morning everyone.
So this is really so such so wonderful to see everyone here and to meet and get to know the Calabrai family. But right now my job is to introduce our speaker. So it is my absolute honor to introduce my colleague and friend, Doctor Yanni as our guest lecturer for the Paul Calabresi Memorial Lecture Series. Doctor Yanni earned his MD as well as PhD degrees from the University of Pennsylvania. He then completed postgraduate training in internal medicine at Brigham and Women’s Hospital and in Medical Oncology at Dana Farber Cancer Institute.
He’s currently the director of the Lowe Center for Thoracic Oncology and the scientific director of the Belfer Center for Applied Cancer Science. And he’s also professor of Medicine at Harvard Medical School and the David M Livingston, MD Chair at Dana Farber.

So it was at Dana Farber that I first met posse when I was a fellow. It was several years ago now as we were reminiscing about last night, I worked in his clinic and still now, you know as we both see patients with lung cancer, we sometimes still share patients.
And I can personally attest that he really is a fantastic oncologist who goes above and beyond for every single patient. So I’m going to now turn over to Katie Politi to tell you a bit about Doctor Yanni’s remarkable scientific contributions and PASI, I’m really looking forward to your lecture.

Bon giorno E benvenuti attuti specialmente a la familia calabresi E aldotor pasi Yanni. As I said, good morning and welcome to everybody and especially to the Calabrese family and to Doctor Pasiyani Today.
The advances in lung cancer treatment over the past 20 years have been remarkable and are contributing to a reduction in lung cancer deaths that we’ve seen in recent years. Doctor Yanni’s research has played a central and critical role in contributing to the better outcomes for patients with lung cancer that we see today. His main research interests include studying the therapeutic relevance of oncogenic alterations in lung cancer. He was one of the co-discoverers of epidermal growth factor mutations in lung cancer and has pioneered the development of therapeutic...
strategies for patients with EGF receptor mutant lung cancer.

His lab based and clinical research has also focused on other oncogenic driver subsets like those for patients whose tumors harbor K Ras mutations.

As you will see today, Doctor Yanni’s laboratory research is at the forefront of addressing major challenges in lung cancer and sets the stage for advancing approaches for clinical treatment of the disease.

Thank you Pasi for being here today. It’s a pleasure to have you here for this lecture.
We’re going to take a picture with a Reef before we start because and for inviting child raising family to come up. I’m also going to ask Lori Pickens, our Senior Vice President from Smile, to join us and we’ll take the obligate picture that will be in direct connect and we’re how do you want us? How was he going to do that? So why have to come? The screen, by the way, went to a shoe up. What invited speaker knows they only get 15 minutes to clock,
but we will have. By the way, at the end, we're having mentorship testing. With any training you would like to say we're going to have all the images. Could we kill this just for a second? Just for a quick second? Sure. Thanks. Good luck at lunch. Thank you so much. Thank you. I'll put it over here. Thank you for those wonderful introductions and thank you Roy and entire team for inviting me here. And thank you for the Calabrese family. It was lovely to meet all of you yesterday.
So I will focus my lecture today on a specific area of lung Cancer Research that we call drug tolerant persisters and you’ll see what that all means in a few moments. These are my disclosures. I work with lots of companies to try to develop new therapies and hence the disclosures. So as Doctor Goldberg mentioned, lung cancer therapies have changed quite a bit and we think of lung cancer, especially lung adenocarcinoma, which is the most common form of lung cancer today as a cancer that
harbors potentially targetable genetic alterations shown in this pie chart. And if we actually look at what has been approved as therapies for these different alterations, we actually have a large number of therapies and more coming all the time approved for specific subsets of lung cancer. And so when we see patients in the clinic, one of our first questions is to try to understand does the cancer in that individual harbor one of these genetic alterations that we could then use one of the therapies on the right hand side or enroll that patient into a
clinical trial that may be evaluating a new therapy or a therapeutic combination. And the therapies are successful. However, they still don’t cure patients with advanced lung cancer. They’re better than what we would have had 2025 years ago, which is chemotherapy, but we still need to continue to do better. And So what typically happens, and this is an example of a patient with a lung cancer and he’s treated with a targeted therapy and you can see almost all of the cancer disappears, but then it ultimately comes back. And what I’ll focus my discussion today...
and what my lab has focused a lot is trying to understand why does it almost, almost completely disappears, but not completely disappear. And if we made this sort of intermediate state completely disappear, would our therapies be more effective? So let’s look at it at a kind of A at this level. So, an example of a cancer we call this this sort of intermediate state the the persistor state or the drug tolerant persistor state out of which cancer various resistance mechanisms that we
can detect clinically ultimately arise.

00:10:57.160 --> 00:10:58.693 Sometimes resistance mechanisms can pre-existing cancers and when you treat them with therapies they can outgrow it and develop resistance in that way.

00:11:01.248 --> 00:11:04.070 But this is definitely as shown in those scans before happens as well and so how can we do better well we can develop therapies that are more effective at this initial therapy to eliminate this intermediate state or we can treat or figure out what make what’s unique about this.
intermediate state and how could we eliminate it and ultimately delay or prevent resistance. So one and as you heard from the introduction, I, I focus on EGFR mutant lung cancer, which in that pie chart is not quite the biggest, sort of the second biggest piece of the pie. And we were involved in that initial discovery and have subsequently tried to develop therapies for patients who are treated with EGFR inhibitors. And one of the things that we're recently involved in was asking
can we use another therapy such as chemotherapy that we commonly use in lung cancer in combination with an EGFR inhibitor. And would that in fact lead to a better outcome for patients compared to an EGFR inhibitor alone. And that could be because it's more effective initially or it impacts this intermediate state. And so this is a clinical trial that those of you who treat lung cancer patients are probably familiar with called the FLORA two trial where the standard of care EGF inhibitor ASA mertnib also known as Tagrisso.
was combined with chemotherapy compared to the ASA mertnib alone. And patients got combination chemotherapy and then followed by maintenance chemotherapy and ASA mertnib. And this trial turned out to be a positive in terms of progression free survival sort of delaying the likelihood of recurrence from or disease growth from lung cancer significantly depending on how it was looked at by the investigators or by blinded review. It delays that by about nine months which has clinical implications as well.
It was especially effective in patients whose cancer had metastasized to the brain. This difference is larger but even in patients where that wasn’t the case, it was effective.

And if we look at the common types of EGFR mutations, about 50% are these Exon 19 deletions and 50% are these L158 arm mutations. In both cases chemotherapy improved the outcome of the patients. It’s too early to know whether this improvement translates into patients living longer.
We'll hopefully have some updates later on this year on that. But it did delay the 2nd progression free survival. So the time of so patients who got chemotherapy and an EGFR inhibitor first even if they got subsequent therapy it's still that was still effective. They they had a longer durability of benefit than if they just started the EGFR inhibitor. Now if we look at kind of trying to understand what is chemotherapy doing now it turns out
that this is the EGFR inhibitor alone and this is chemotherapy, these look very similar. This is, these are all individual patients and the degree or or so this is what we call a waterfall plot and these are all patients were measuring their tumor shrinkage. And what was maybe disappointing is that even with the addition of chemotherapy the the maximum or median best tumor shrinkage was 50% in the EGFR inhibitor and only 52.6% when you added chemotherapy. However, the durability of that shrinkage
00:15:29.360 --> 00:15:30.587 was much longer,
NOTE Confidence: 0.663055519090909

00:15:30.587 --> 00:15:33.041 about nine months longer if you
NOTE Confidence: 0.663055519090909

00:15:33.041 --> 00:15:35.422 had chemotherapy compared to the
NOTE Confidence: 0.663055519090909

00:15:35.422 --> 00:15:36.678 EGFR inhibited by itself.
NOTE Confidence: 0.663055519090909

00:15:36.680 --> 00:15:39.280 But it still means that there are
NOTE Confidence: 0.663055519090909

00:15:39.280 --> 00:15:42.400 cancer cells that are able to
NOTE Confidence: 0.663055519090909

00:15:42.400 --> 00:15:44.424 survive despite EGFR inhibition and
NOTE Confidence: 0.663055519090909

00:15:44.424 --> 00:15:47.503 and and and this is an area that we
NOTE Confidence: 0.663055519090909

00:15:47.503 --> 00:15:49.283 have focused pre clinically quite
NOTE Confidence: 0.663055519090909

00:15:49.283 --> 00:15:52.009 a bit and asked the question what
NOTE Confidence: 0.663055519090909

00:15:52.009 --> 00:15:54.391 sort of dictates the dichotomy of
NOTE Confidence: 0.663055519090909

00:15:54.400 --> 00:15:57.060 a of a of a of a cancer cell from
NOTE Confidence: 0.663055519090909

00:15:57.144 --> 00:15:59.616 dying versus surviving these cancers
NOTE Confidence: 0.663055519090909

00:15:59.616 --> 00:16:01.356 that have these EGFR mutations.
NOTE Confidence: 0.663055519090909

00:16:01.360 --> 00:16:02.560 This represents a cancer and
NOTE Confidence: 0.663055519090909
these are individual cells.

All of the individual cells have the EGFR mutation.

So it's not like the ones that survive don't have the EGFR alteration, they do but they figure out ways to survive whereas others die.

And several years ago we recognize that one of the downstream pathways from EGFR map, kinase pathway are here as measured here it's on here it's off but within a few days it comes back on and if you block this pathway with a MEC inhibitor here trimetinib,
you can prevent that from happening.

So why is that important?

Well, the way EGFR inhibitors cause cancer cells to die is they down regulate this pathway as I've shown here that bath that leads to up regulation of a proapoptotic protein called BIM and then leads to cell death.

And so now EGFR inhibition is decoupled from down regulating of this pathway.

Now you've provided a way for the cells to survive, turn this pathway on and and survive.

And so here we can block it with a
drug trimetinib, our MEC inhibitor. And we’re trying to evaluate this in the clinic by doing a clinical trial combining an EGFR inhibitor here with a MEC inhibitor called solumettinib. And here we have to give it intermittently 4 days on, 3 days off because when these drugs are given by themselves, they have side effects, typically skin side effects and fevers and other side effects. And so we can’t give both the EGFR inhibitor and the MEC inhibitor every day.
outcome that we saw in the laboratory. Setting remains to be seen. Now despite doing those two therapies, if we look at cells under the microscope, they're still surviving even when we add those two combinations together. And if we analyze the cells that are after one day of giving the drugs or 21 days after giving the drugs, we can see that all of the sort of EGFR and pathways are turned off including ERC because we're using that the MEC inhibitor here. If you withdraw those,
if you then wash out the drugs, the cancer actually regrows that we call rebound cells and all of those pathways are once again on. And so we had wondered how is it that they survive and they survive through up regulating another signaling pathway called the Hippo signaling pathway, namely a protein called Yap that normally when it’s turned on or up regulated which happens in response to EGFR and MEC inhibition, it turns off the expression of a pro apoptotic sensitizer called BMF. And so if you now block this
in any way genetically deleted or use drugs against this, you now up regulate this protein. It can release more of the apoptotic proteins namely BIM from anti apoptotic proteins and it can shift cell survival to cell death. And so that’s another. So it’s basically another counter regulatory mechanism by which cancer is used to survive. And this is just to prove that you actually need if you use genetic tools to knock out this BMF, you don’t see the increased
cell death here compared to if it’s not knocked out.

And the good thing is there are now companies that make TEED inhibitors.

This Yap protein interacts with another protein called TEED and there are multiple companies that are making these inhibitors and if we use these inhibitors, here if we measure cell death in red, when we add one of these inhibitors, they increase cell death from blue to red and we hope that this is clinically meaningful.

They’re being mostly tested in initially in malignant mesothelioma,
but they there are hopes that these will move towards testing in lung cancers as well. So I mentioned the two kind of regulatory pathways. We then wanted to ask another question by studying this state and ask is there something that we can you know if we these are to enhance the initial effect of the therapies. I’ll shift to talking about this cell state and ask are these the unique vulnerabilities within this actual cell state. And when we did this prior study
where we

found this Yap teed pathway,

we recognize that the cells that

survive in after a inhibition with

an EGFR inhibitor or any other

inhibitor in the right genetic context,

they have features of cellular senescence,

so aging cells and it it doesn’t

matter how you characterize them,

they all have this is a,

they’re often they stain blue and

this beta galactosidase stain

and they have other features that

are all found in these cells.

Now it’s not true cellular senescence

because true senescence is irreversible
unfortunately as all of us are aging.

But this is a reversible state because as I mentioned earlier

if you take the drugs off, the cancer cells will start to grow.

And there is a whole field of developing drugs trying to treat senescent cells and they’re often referred to as Senalytics.

And what we so we wanted to do is first treat our cancer cells with an EGFR inhibitor and then treat him with another drug to ask can we in this red example can we find drugs that would specifically eliminate
or be toxic to those cells that are in this state. And when we look through and screened all of them, the ones that scored in the top are inhibitors of BCLXL which is an anti-apoptotic protein. So by inhibiting that you can again shift cells more to dying as opposed to surviving and this is enriched in the senescent state.

So if that’s true then we should be able to show that experimentally and so we first did this experiment where we took mice that have a xenograft of an EGFR mutant cells. We treated them with a control or
00:23:04.613 --> 00:23:06.851 with the EGFR and MEC inhibitor

00:23:06.851 --> 00:23:09.039 combination for three weeks and after

00:23:09.039 --> 00:23:11.488 three weeks we split half the mice

00:23:11.488 --> 00:23:13.952 to continue the EGFR MEC inhibitor or

00:23:13.952 --> 00:23:16.372 added a BCLXL inhibitor Nabita Clex.

00:23:16.372 --> 00:23:20.320 And then we treated for another three weeks

00:23:20.320 --> 00:23:22.040 and then we stopped all the drug treatments.

00:23:22.040 --> 00:23:25.678 And we asked is there is there a

00:23:25.678 --> 00:23:27.880 difference in growth regrowth of the of

00:23:27.880 --> 00:23:30.785 the cancer in the in the model that just

00:23:30.785 --> 00:23:33.333 got the EGFR MEC inhibitor compared to

00:23:33.333 --> 00:23:35.670 the one that got the BCLXL inhibitor.

00:23:35.670 --> 00:23:39.310 Because if we if if our hypothesis

00:23:39.397 --> 00:23:41.615 is correct at this state that persistent

00:23:41.615 --> 00:23:43.304 state has been established and if

NOTE Confidence: 0.6015004
they’re sensitive to the nevita clax,

we should eliminate more of the cells and then it should delay the regrowth of the tumor.

And it does a little bit in green here although you could argue that this is probably pretty marginal.

This is so the treatment,

this is the day 42 when we withdraw the drugs and then compare growth.

And here if you look at the individual animals,

you can see that most of them still grow back although there are some that are completely eliminated.
So we were wondering why may that be the case and one possibility is, are we delivering the drugs to these persistent cells in an efficient manner. And to get at that problem, we’ve worked with AbbVie, a pharmaceutical company that has developed an antibody against EGFR that’s coupled to a BCLXL inhibitor. So this is a more of a targeted way of delivering the BCLXL inhibitor specifically to cells that express...
EGFR like the cancer cells that we’re interested in And it and that has the advantage of avoiding potential systemic toxicities because if you just give the inhibitor by itself, one of the toxicities that’s been seen in the clinic is thrombocytopenia or lowering of platelet counts because this protein is important for maturation of the platelets. And so if you give the drugs will there go to the tumor and to the bone marrow, you’ll start to see patients platelet counts decrease. And this is just to show that in from ADVI, if they use a small molecule inhibitor,
00:25:31.000 --> 00:25:33.040 here’s normal platelets, they go down.

00:25:33.040 --> 00:25:35.238 But if he uses antibody drug conjugate

00:25:35.238 --> 00:25:37.713 since this is not cleaved normally

00:25:37.713 --> 00:25:40.280 except when it’s internalized into the cell,

00:25:40.280 --> 00:25:42.020 you don’t see that much

00:25:42.020 --> 00:25:46.040 of a platelet reduction.

00:25:46.040 --> 00:25:48.296 So in ABB Vie’s experiments

00:25:48.296 --> 00:25:50.795 when they’ve done given the EGFR

00:25:50.795 --> 00:25:53.110 inhibitor together with this antibody

00:25:53.110 --> 00:25:55.501 drug conjugate from the beginning,

00:25:55.501 --> 00:25:57.936 they can certainly delay the

00:25:57.936 --> 00:26:00.314 regrowth of cancer cancers in

00:26:00.314 --> 00:26:02.399 in these two different models.

00:26:02.400 --> 00:26:03.340 But that wasn’t exactly the

00:26:03.340 --> 00:26:04.280 question that we were after.
We were after this question, what happens in that persistent state. So we kind of redid that experiment here using the EGFR inhibitor alone where we then after 21 days half the mice will continue the EGFR inhibitor alone, half the mice will continue the FRBCLXL antibody drug conjugate for another three weeks and then we withdraw the drugs and follow outgrowth and here we see a much more dramatic difference and green is the double combination. You can see that here individual animals. So it’s much more impressive than than
than using the nevitoclax alone and the animals tolerate it quite well. There are some some over long periods of time. This is like you know six months later we can look at the animals and not all of them are cured. Some of them do regrow and we can detect the regrowth by using antibodies that specifically detect the mutiny GFR protein. Sometimes we see immune infiltrates and if we compare.
So we can cure some of the animals
with the EGFR inhibitor alone,
but we can cure many more
when we add this other agent.
In the middle of treatment is
another model that kind of
shows the same phenomenon.
Unfortunately, they also do start to regrow
after a period of time and so.
So we see that some mice are cured,
others are not and that could be for
lots of reasons, it’s a duration of
treatment important in the clinic.
We would typically continue a second
therapy for much longer periods of time
than we did in the animal experiment.
And of course there are other proteins, other antipoptotic proteins that can sort of compensate for BCLXL inhibition such as MCL one. And that may be the reason that we’re seeing some of those relapses. But ultimately we want to ask is this, is this something that can be applied in the clinic? It’s called a BVAB BV637 made by Avi. And at this year’s ESMO meeting,
00:28:26.496 --> 00:28:29.664 my colleague Julia Rotor from Dana
NOTE Confidence: 0.71174131875
00:28:29.664 --> 00:28:32.046 Farber presented the clinical data
NOTE Confidence: 0.71174131875
00:28:32.046 --> 00:28:34.944 of giving this agent by itself or
NOTE Confidence: 0.71174131875
00:28:35.029 --> 00:28:37.193 in combination with chemotherapy
NOTE Confidence: 0.71174131875
00:28:37.193 --> 00:28:39.234 or with with awesome mertinib.
NOTE Confidence: 0.71174131875
00:28:39.234 --> 00:28:41.460 So here it’s given monthly and the
NOTE Confidence: 0.71174131875
00:28:41.522 --> 00:28:43.612 awesome mertinib is given every day.
NOTE Confidence: 0.71174131875
00:28:43.612 --> 00:28:46.380 And the good thing is that the combination
NOTE Confidence: 0.71174131875
00:28:46.446 --> 00:28:48.596 is actually quite well tolerated.
NOTE Confidence: 0.71174131875
00:28:48.600 --> 00:28:50.536 There’s some liver function
NOTE Confidence: 0.71174131875
00:28:50.536 --> 00:28:52.956 abnormalities that you can see.
NOTE Confidence: 0.71174131875
00:28:52.960 --> 00:28:55.480 But no, there was no major interactions,
NOTE Confidence: 0.71174131875
00:28:55.480 --> 00:28:57.435 there’s no major platelet decreases
NOTE Confidence: 0.71174131875
00:28:57.435 --> 00:28:59.989 as we’d expect from the preclinical
NOTE Confidence: 0.71174131875
00:28:59.989 --> 00:29:04.516 data and no bad toxicities that would
NOTE Confidence: 0.71174131875
00:29:04.516 --> 00:29:06.611 get us worried about potentially
00:29:06.611 --> 00:29:07.956 moving this combination forward.

00:29:07.956 --> 00:29:10.721 So our plan is to try to move that forward and use it in that same scenario and patients that we saw in the mouse models.

00:29:13.165 --> 00:29:15.319 And in fact in that presentation, these were all patients that have been treated previously with Asamertinib.

00:29:17.360 --> 00:29:18.960 in the mouse models.

00:29:18.960 --> 00:29:21.360 And in fact in that presentation, these were all patients that have been treated previously with Asamertinib.

00:29:21.360 --> 00:29:23.551 these were all patients that have been treated previously with Asamertinib.

00:29:23.551 --> 00:29:24.880 treated previously with Asamertinib.

00:29:24.880 --> 00:29:27.246 and in some of those patients that combination actually led to tumor shrinkage which was very nice to see.

00:29:27.246 --> 00:29:28.778 combination actually led to tumor

00:29:28.778 --> 00:29:32.264 shrinkage which was very nice to see.

00:29:32.264 --> 00:29:35.719 and encouraging to see that.

00:29:35.719 --> 00:29:40.640 forward for clinical development.

00:29:40.640 --> 00:29:43.384 So another, so I talked about that.

00:29:43.384 --> 00:29:45.800 vulnerability and then the other option,
other thing that we’re doing is asking of this sort of intermediate state, are there novel targets that could be expressed in this state that we could go after with therapies that are in the clinic or therapies that need to be developed for clinical application. And so we’ve done some RNA sequencing analysis and untreated cells and cells that are in this sort of persist or state focusing on specifically looking at cell surface proteins as targets. And for many cell surface proteins there are antibody drug conjugates which are that are in the clinic.
not the BCL XL inhibitor that I showed, but to chemotherapy and so having a more sort of targeted way of delivering chemotherapy to two cells. And these are just three of them. And we see them that they’re both sort of enriched in that sort of state after treatment with an EGFR inhibitor here. You can see them by Western blotting. You can see in these EGFR mutant cancers this black band is this TROP 2 protein that’s enriched after treatment with an EGFR inhibitor. This is full R1 which is a folate receptor that’s also increased and
it’s not just limited to EGFR. Here are cells with other genetic alterations and ALK rearranged cell lines. We’re treated with an ALK inhibitor. You can see the same thing, a Med amplified cell line treated with a Med inhibitor or K Ras mutant cell line treated with AK Ras inhibitor. You can see the the same things and and some cell line models,
some are patient derived models to study that state that we mentioned earlier in the presentation where we initially studied it from cells and grown in plastic but here we can study it from animals and here you can see the animals are treated with EGFR inhibitor, EGFR MEC inhibitor and they have these very nice responses.

So the time of this maximum response we dissect out the kind of the residual area where the tumor is. We purify the tumor cells and can do all different types of
00:32:09.280 --> 00:32:11.480 analysis on the tumor cells to ask.
NOTE Confidence: 0.793071963333333
00:32:11.480 --> 00:32:14.324 This has also happened in vivo as opposed to just in a tissue culture model.
NOTE Confidence: 0.793071963333333
00:32:14.324 --> 00:32:17.000 And so here's one example of different models treated with Asamertinib,
NOTE Confidence: 0.793071963333333
00:32:20.656 --> 00:32:22.640 Rasamertinib in the MEC inhibitor.
NOTE Confidence: 0.793071963333333
00:32:22.640 --> 00:32:24.160 This is the what the tumors look like when we dissect them out in the minimal residual state.
NOTE Confidence: 0.793071963333333
00:32:28.002 --> 00:32:33.760 And if we look for expression of trope 2, we can see that it’s a membrane
NOTE Confidence: 0.793071963333333
00:32:35.839 --> 00:32:36.433 bound protein.
NOTE Confidence: 0.793071963333333
00:32:36.440 --> 00:32:39.436 So you can see it expressed here
NOTE Confidence: 0.793071963333333
00:32:41.108 --> 00:32:43.359 in the untreated models, although you do see some expression
NOTE Confidence: 0.793071963333333
in the untreated models.

And if we quantify this, the models tend to have some baseline expression which is then enhanced with e.g. FREGFR MEC treatment and it kind of varies a little bit from model to model. This is the same experiment for this folate receptor. It seems to be much you don’t find it in the untreated but you do find it in the treated one. So we like these kinds of examples because the hope would be that this is something that’s specifically induced in the tumor cells and
hence any therapeutic strategy should be hopefully have a wider therapeutic index that it’s targeting the tumor and not normal tissues. But wait to see that and here it’s we look at it by RNA sequencing, same idea, we can look for these different cell surface proteins that are up regulated and for which there are antibody drug conjugates. And we also have a trial where we’re trying to understand this. This actually happened in patients and so this is a trial, a very straightforward trial where newly diagnosed lung cancer patients
were treated with Osamerton, they’ve been the EGFR inhibitor in the primary goal of the trial was to study how do cancers develop resistance to Asamerton when it’s clinically visible. But what we built into this trial is that during the sort of maximal time that the person has had a response to therapy, we biopsy that area if we can find it and do analysis to see can we find these proteins expressed that I showed in the preclinical models. This is just an example of a patient. Here’s two months of ASA Merton if not the most dramatic reduction but and
here you may able to see the biopsy needle,

we're biopsy in the individual and a study only has on treatment biopsy.

So we don’t have the pre treatment to compare it to.

But at least by single cell RNA sequencing in the on treatment biopsies we can find a cluster of tumor cells that express trope here in this case trope 2.

So at least we think that this is has some real relevance in patience and are trying to validate it further.

So what is Trope 2?

Trope 2’s may be familiar for our clinical audience,

but it’s a intracellular calcium
NOTE Confidence: 0.862701431538462
00:35:10.400 --> 00:35:12.640 signal transducer that’s over
NOTE Confidence: 0.862701431538462
00:35:12.640 --> 00:35:15.520 expressed in many epithelial cancers.
NOTE Confidence: 0.862701431538462
00:35:15.520 --> 00:35:18.397 There are agents that target trope 2.
NOTE Confidence: 0.862701431538462
00:35:18.400 --> 00:35:21.520 Here’s an antibody linked to A
NOTE Confidence: 0.862701431538462
00:35:21.520 --> 00:35:24.305 chemotherapeutic agent in red here
NOTE Confidence: 0.862701431538462
00:35:24.305 --> 00:35:26.533 that’s still infused intravenously
NOTE Confidence: 0.862701431538462
00:35:26.533 --> 00:35:29.405 and then binds the tumor cells and
NOTE Confidence: 0.862701431538462
00:35:29.405 --> 00:35:30.945 then this chemotherapeutic agent
NOTE Confidence: 0.862701431538462
00:35:30.945 --> 00:35:33.197 is internalized and cleaved in the
NOTE Confidence: 0.862701431538462
00:35:33.197 --> 00:35:35.440 tumor cells like a Trojan horse.
NOTE Confidence: 0.862701431538462
00:35:35.440 --> 00:35:38.900 And then specifically can can
NOTE Confidence: 0.862701431538462
00:35:38.900 --> 00:35:40.520 kill the tumor cells.
NOTE Confidence: 0.862701431538462
00:35:40.520 --> 00:35:42.344 And if we use this agent
NOTE Confidence: 0.862701431538462
00:35:42.344 --> 00:35:43.560 in lung cancer patients,
NOTE Confidence: 0.862701431538462
00:35:43.560 --> 00:35:45.744 you can see about 1/4 of patients
NOTE Confidence: 0.862701431538462
have tumor shrinkage and some of them
NOTE Confidence: 0.862701431538462
have more dramatic tumor shrinkage.
NOTE Confidence: 0.862701431538462
This is given to a wide variety
NOTE Confidence: 0.862701431538462
of patients with lung cancer.
NOTE Confidence: 0.862701431538462
What we’ve learned over the last
couple years is that it works
perhaps particularly well in cancers
whose cancers have genetic alterations,
about a third of them
most of these have EGFR mutant cancers
although there are others in there as well.
And but this year’s ESMO meeting
or last year’s ESMO meeting, this was studied in more detail. And patients that have an EGFR mutation, they tend to have a greater response than cancers that have other genetic alterations for reasons that nobody understands yet. But it’s something that we’re keenly interested in investigating. So we then use that same sort of in vivo model and ask the experiment if we now target this stroke two protein after this persistent state has been established, doesn’t matter. So again treat the mice with asamertinib,
some are, some continue on asamertinib
and some are given this troph
2 antibody drug conjugate which
is approved in breast cancer,
not lung cancer.
And in fact the clinical trial and
lung cancer just failed unfortunately
and again treat him and then we
withdraw the drugs and there is
a little bit of a difference.
It’s not humongous,
but there’s a little bit of a difference
in the tumors that got treated with
a Trop 2 antibody drug conjugate.
On the other hand,
they all start to regrow.

So we didn’t really cure any of the mice here using this approach.

So this Trop 2 protein expression increases following therapies that directed at the right genetic alteration in lung cancers. Adding this antibody drug conjugate once this tolerant state has been formed didn’t really eradicate these cells because otherwise the cancers wouldn’t have been able to grow back.

And so where do we go from here? There are other antibody drug conjugates targeting this.
protein that may be more potent, which could be an issue here, one made by Dai Ichi and being developed by Dai Chi and AstraZeneca called DS1062A. Do we need to increase the duration of the treatment? Is that an issue here or can we develop some novel strategies here and I'll show you one novel strategy that we're evaluating that is developing CAR T cells directed at trope 2. So chimeric antigen receptor T cell therapy type of immune therapy is being used in lots of hematologic malignancies and has done wonders there on a therapy.
Just this strategy in general has struggled in solid tumors and part of the issue is that you’re targeting you have to target a specific cell surface protein. If that cell surface protein is also present in normal tissues, then you’re delivering this effective therapy to normal tissues and that can lead to a lot of toxicities. And so you need to try to identify two unique proteins, tumor antigens, proteins present on the surface of tumor cells that are not found on
normal cells and that’s remained a challenge in the solid tumor field. And this is work we’ve done with Eric Smith and Elliot Brea at Dana Farber. So this just shows you what these things look like. And so if we use these cells in again in a tissue culture model and we take those EGFR immune cancer cells and genetically remove trope 2. So the target of where the antibody is supposed to bind the cells do nothing. Here in red and in green is a non-specific or a a CAR T cell against the B cell antigen that isn’t expressed at all. So if you knock it out or make a CAR
T cell against an irrelevant protein, nothing happens. If you enter these knockout cells, replace the normal form of tropo too, and now you can see less cells survive, or in the endogenous cells, less cell survives versus targeting AB cell antigen doesn’t do anything. We of course wanted to make sure that the EGFR inhibitors weren’t toxic to these CAR T cells and they’re not except when you get to very high concentrations. So then we then we asked the experiment of first treating them with the EGFR
inhibitor and tissue culture model and
then to set up that drug tolerance state
and then expose them to the CAR T cells.
And.
And similarly, if you’ve knocked out trope 2,
nothing happens.
And in the endogenous EGFR immune cells,
they’re very effective,
nothing happens.
And if you’ve replaced the
normal into this knockout cell,
replace the normal form of trope 2.
So now it’s expressed.
Now they’re once again effective
like in the normal situation.
So we do think it’s doing what we expected to be doing at least in vitro. And we’ve now also again finally taken the same experiment and are starting to do it in vivo.

Treat the tumors for 10 days or 21 days. Randomize them to continue EGFR inhibition. Use the continue with EGFR inhibition and the trope to antibody drug conjugate or a CAR T cell against the B cell antigen or against trope to just delivered once and then ask what happens to these animals.

So they’re delivered here. This is the schedule for the ADC.
delivery and then the CAR T cells are delivered also here at day 21. And you can see that the ones that are treated with the EGFR inhibitor alone all managed to regrow. The ones that are treated with the targeting an irrelevant protein also regrow and purple behind it. And the ones that are treated with the CAR T cell or in this case the ADC, the Sazotuzumabe and Goba T can’t have the separation. And if we look at this long term, we certainly see that the ones that receive the trope 2 CAR T cell have a much better outcome.
There are some escapers here and we're trying to understand why do they escape therapy. All of the ones treated with the ADC like in our prior experiments start to regrow. Similarly with the EGFR inhibitor by itself and and also most of the ones that are treated with irrelevant or B cell antigen CAR, T cell also start to regrow as we'd expect. So I talked about this drug tolerant persistent state that can give rise to a broad range of actual drug
resistance mechanisms and it’s really one step why are one reason, not the only reason but one reason why are effective targeted therapies, precision therapies in lung cancer although effective they’re not effective forever, they ultimately resistance happens in most if not all patients. And this state, what I’m trying to was trying to convince you is this state has some unique biologic properties and expressed potentially novel cell surface targets which can be leveraged therapeutically. And if we prevent the formation of this state or specifically treat the state,
we may be able to extend the benefits of our genotype directed therapies and lung cancers and maybe in other cancers. But this needs clinical validation and of course the issue that I mentioned that some of these proteins that are expressed in these drug tolerant states also expressed in normal tissues which may limit the therapeutic window and may limit the therapeutic window and again one reason why or 111 big reason why clinical validation is needed. So I just wanted to thank just acknowledge the many members of my laboratory who’ve been worked on these various projects.
middle are my long term collaborators in this field, Nathaniel Gray who’s a medicinal chemist, Mike Eck who is a structural biologist, biochemist and Kwak Wong who does animal models of lung cancer. We've worked, had the pleasure to work together for the last 10 years or so except during that time both Nathaniel and Kwak left Dana Farber. But we still continue to work together and just submitted APO one together. So we’ll hopefully be able to do this. The clinical, we have a lot of wonderful clinicians
and clinical trialists who will run the clinical trials that I mentioned to you. That couldn’t be done without our clinical research staff and patients and families who participate in clinical trials or translational research undergoing on treatment biopsies which may not benefit them directly but may ultimately help develop new therapies.

We use a lot of bioinformatics in our analysis and with that couldn’t be done without the bioinformaticians, the Belfer Centre that I helped run. These are many of the members are there and of course we need to have
collaborators in the pharma industry
NOTE Confidence: 0.8474694
who are developing many of these
drugs to be able to
carry them out and hear some
collaborators from AstraZeneca,
NOTE Confidence: 0.781017591
Daiichi Sanchio and AbbVie.
NOTE Confidence: 0.781017591
My collaborator Dave Barbie on
Eric and Dave
works with Eric and Dave
on the car T cell studies.
NOTE Confidence: 0.781017591
I just want to acknowledge them.
NOTE Confidence: 0.781017591
And of course, none of the work
would be possible without funding.
NOTE Confidence: 0.781017591
And these are many of the
NOTE Confidence: 0.781017591
funding agencies that have
supported the work over the years.
So I will stop there and happy to take any questions. Thank you again for the invitation to be here.

Thank you so much, Posse, for really a fantastic talk. It was so clinically relevant and you’re doing amazing work to really advance this field.

So thank you again for all of that and for being here. So as is tradition, the first question goes back to Vito Calabrese. I don’t know. All right. OK.
even if I have nothing to say.

But I was wondering whether in other
types of cancers like Melanoma which
got treated from nothing and then had
the same intermediate stage developed
where there were some cells of this
sort and they found ways of going
after them or whether there was a
total treatment from the first time. So
depends a little bit on the type of therapy.
But this sort of intermediate state
does exist in other cancers if they’re
especially if they’re treated with the
targeted therapies that I mentioned.
I think the difference in
Melanoma is that it’s a very,
00:47:26.040 --> 00:47:28.770 it’s a cancer that we can effectively
00:47:28.770 --> 00:47:30.917 treat with immune therapies that
00:47:30.917 --> 00:47:33.270 are already exist and were developed
00:47:33.270 --> 00:47:34.920 in Melanoma and other cancers.
00:47:34.920 --> 00:47:36.800 They do work in lung cancers as well.
00:47:36.800 --> 00:47:38.728 They just don’t work in the lung cancers
00:47:38.728 --> 00:47:40.295 that have these genetic alterations
00:47:40.295 --> 00:47:42.353 where we use these targeted therapies.
00:47:42.360 --> 00:47:43.836 And so that's why we need
00:47:43.840 --> 00:47:44.502 different approaches.
00:47:44.502 --> 00:47:46.157 But it isn’t this example.
00:47:46.160 --> 00:47:47.760 This sort of pattern isn’t
00:47:47.760 --> 00:47:49.040 unique to lung cancer,
00:47:49.040 --> 00:47:51.000 does happen in other cancers as well.
00:47:53.080 --> 00:47:55.735 Hi, I’m. I’m Steve Calabresi, Dr.
Calabresi’s son. And I’m a law professor. So this question may not be thoroughly relevant, but my father had a cancer of the tongue in 1975 on the left side of the tongue and was given a 15% chance of surviving. He ended up living another 25 years. The way he treated the cancer of the tongue was to have surgery on his tongue and to have the glands on the left side of his neck removed, which turned out to have cancer cells in them. He had chemotherapy, radiation therapy with radioactive needles in his tongue, and he even used, in 1975,
a primitive form of immunotherapy.
And his idea was to throw everything, basically.
And so I wondered with these persistent can cancers,
can you once you reduce the size of the cancer to a smaller location,
is there any chance of gaining anything by surgically removing it.
Obviously microscopic cancer cells might remain but maybe those would could be targeted by chemotherapy or
yeah so in in the, in the EGFR example and Roy knows is very well since he led the the,
the trials patients who have earlier stage lung cancer which we can potentially cure with surgery although it can still recur. We now use these effective like the EGFR inhibitor as an adjuvant. So after surgery patients may get chemotherapy and then they get the EGFR inhibitor for multiple years there. We know that that not only reduces the likelihood of the cancer coming back, but it makes people live longer. Now whether whether it ultimately cures those cancers, I think we don’t know yet, but at least the early signs are
all going in the right direction.

So yes, absolutely we're trying trying to take what we learn in studying patients with advanced lung cancer and moving the effective therapies into earlier settings where we can hopefully cure more patients with the disease as long as we can find the cancers in the earlier stage which remains a challenge still.

really nice talk. I'm wondering if drug therapy is acquired through somatic mutations or if there are
pre-existing cells that then grow out that account for the. Yeah, both can happen and there's and certainly there are examples in lung cancer and then EJFR space where you can find the, you know, you know one in a million cells you can find the resistance mechanism cancer with a resistance mechanism already there and then over time it gets selected for. But the other way around, the other other is also true that you may not find it, but it's this intermediate state for whatever reason then is denied us for many
Different resistance things to evolve, and part of the reason to go after that. But both do exist. Both both paths to resistance are possible. Doesn’t mean they can’t coexist either. Hi, Pasi, it’s good to see you and thanks for coming. It’s beautiful work. I wondered if in the studies you use the combination of BCLXADC and ASA Mertonib, did you add, did you do any studies combining that with the MEC inhibitor because it looks like...
like that’s your preclinical data with support that triplet.

Yeah, We didn’t, we didn’t. And part of it is that it’s, it’s tough to take the MEC inhibitor combinations forward clinically because of the MEC inhibitor toxicity. And so we wanted to stick to strategies that we could ultimately test in the clinic in the form of a clinical trial. And as you said, we’re doing a trial of ASA, Merton and Ben Celimetin, but even that and even giving it an intermediate or intermittent dose levels, not everybody can tolerate it.
00:52:04.840 --> 00:52:10.072 The MEC inhibitor toxicity adds up over time.

00:52:10.072 --> 00:52:10.520 Thanks.

00:52:12.360 --> 00:52:13.770 I’m going to ask a question

00:52:13.770 --> 00:52:15.241 as I walk over here POSI.

00:52:15.241 --> 00:52:17.169 I think you know one of the studies

00:52:17.169 --> 00:52:19.086 that I was really struck by is the

00:52:19.086 --> 00:52:20.750 the study that you did where you

00:52:20.750 --> 00:52:22.400 buy up did on treatment biopsies.

00:52:22.400 --> 00:52:24.609 I think it’s something we a lot of

00:52:24.609 --> 00:52:26.067 trials have them as optional biopsies

00:52:26.067 --> 00:52:27.936 and I think sometimes we feel it’s hard

00:52:27.936 --> 00:52:29.880 to to have patients go through that.

00:52:29.880 --> 00:52:31.548 I’m just curious your experience in

00:52:31.548 --> 00:52:33.254 the clinic because it’s such important

00:52:33.254 --> 00:52:35.137 samples how how it was talking to

85
00:52:35.137 --> 00:52:36.873 patients about that and getting those
NOTE Confidence: 0.881945735454545
00:52:36.873 --> 00:52:38.080 samples and the importance of those
NOTE Confidence: 0.867367971111111
00:52:39.400 --> 00:52:42.910 most most patients that this
NOTE Confidence: 0.867367971111111
00:52:42.910 --> 00:52:46.564 trial and other trials as you
NOTE Confidence: 0.867367971111111
00:52:46.564 --> 00:52:48.674 mentioned require on study biopsies.
NOTE Confidence: 0.867367971111111
00:52:48.680 --> 00:52:52.905 And I think we’re most of our patients
NOTE Confidence: 0.867367971111111
00:52:52.905 --> 00:52:55.578 are willing to assuming it’s safe and
NOTE Confidence: 0.867367971111111
00:52:55.578 --> 00:53:00.080 the tumors in a location that can be
NOTE Confidence: 0.867367971111111
00:53:00.080 --> 00:53:03.580 biopsied are willing to undergo that.
NOTE Confidence: 0.867367971111111
00:53:03.580 --> 00:53:05.960 You know after we explain to them and you
NOTE Confidence: 0.867367971111111
00:53:05.960 --> 00:53:07.934 know although it may not help them directly,
NOTE Confidence: 0.867367971111111
00:53:07.934 --> 00:53:09.855 it’ll help the development of medicines
NOTE Confidence: 0.867367971111111
00:53:09.855 --> 00:53:11.773 that we’re trying to develop and
NOTE Confidence: 0.867367971111111
00:53:11.773 --> 00:53:14.034 it’ll help others in the future and
NOTE Confidence: 0.867367971111111
00:53:14.034 --> 00:53:16.845 we do we are have been able to
NOTE Confidence: 0.867367971111111
00:53:16.845 --> 00:53:18.000 be successful in that but it is it,
it is optional in most cases
optional typically means not done.
So yeah it remains a challenge
a really great talk
as a radiation oncologist.
One thing I worry about is,
is there evidence of the senesa state
being more or less resistant
initial tumor and clinically it might
be relevant patients got you know
a handful of brain Mets and right
now if they have an EGFR option
do we do radiosurgery upfront,
do we just do EGFR therapy and then
watch wait for it to come back.
When’s the right time to kind incorporate. And there there is, there are studies that are looking at this you know for EGFR therapies, you know patients who have sort of maximal response radiating the sort of the remaining areas and and there are some studies that suggest that that may be beneficial. And we typically have a radiation oncologist see our patients have that they’ve had a maximal response to whatever targeted therapy to ask is it feasible, is it in a location that can
00:54:14.616 --> 00:54:16.777 you know that that is can be done in terms of brain lesions.

00:54:21.840 --> 00:54:23.654 I think as medical oncologists we prefer to have pharmacologic approaches to treat brain lesions,

00:54:25.744 --> 00:54:27.879 although we rely heavily on our radiation oncology colleagues for stereotactic radiation.

00:54:27.880 --> 00:54:30.448 But if we can avoid things like whole brain radiation with using pharmacologic agents,

00:54:30.448 --> 00:54:32.754 for stereotactic radiation.

00:54:31.732 --> 00:54:32.754 But if we can avoid things like whole brain radiation with using pharmacologic agents,

00:54:32.754 --> 00:54:34.833 But if we can avoid things like whole brain radiation with using pharmacologic agents,

00:54:32.754 --> 00:54:34.833 But if we can avoid things like whole brain radiation with using pharmacologic agents,

00:54:34.833 --> 00:54:36.348 whole brain radiation with using pharmacologic agents,

00:54:36.348 --> 00:54:37.515 I think that would be preferable.

00:54:40.400 --> 00:54:43.045 But not all of our agents as you know across the blood brain barriers.

00:54:43.045 --> 00:54:46.860 Posse, thanks so much for
As you know as well as anyone, it's now 20 years since the EGF reputations were discovered. Your lab was of course one of the key labs in that and it's so tantalizing to have these oral agents and patients live longer. But as you mentioned, no one's ever really cured.

So now you've described to us adding different agents in that add toxicity. So my question is going to be about that it really does change the course of a patient's life as you start adding in some of these
toxicities with you have to come in for intravenous infusions exactly.

So my specific question is going to be something we’re interested in here, some of the the pulmonary toxicity we see with these antibody drug targets. Is there anything that’s known about structure function and will there be ways to ameliorate that? Because certainly you take someone with a long life span, but you if they end up having a pulmonary crisis that could be of course very devastating.

Yeah. I don’t think we as a field
00:55:36.696 --> 00:55:39.420 completely understand why some of
these antibody drug conjugates
00:55:39.420 --> 00:55:41.420 give a rise to pulmonary toxicity.
00:55:41.420 --> 00:55:44.240 Or of course it is the, the one of
the more feared toxicities because A,
that can be symptomatic and B typically
00:55:48.300 --> 00:55:52.474 means you have to stop using that treatment,
00:55:52.474 --> 00:55:54.112 even though if it’s been
effective because you don’t want to,
00:55:54.112 --> 00:55:56.158 you know, make the toxicity worse.
00:55:56.160 --> 00:55:58.022 But our mechanistic understanding of
what gives rise to that I think is at
00:56:01.000 --> 00:56:04.330 its infancy still and I think something
00:56:04.330 --> 00:56:07.328 that we should continue to work on.
00:56:07.328 --> 00:56:09.773 And they’re not great models like mice don’t
00:56:09.773 --> 00:56:12.160 get interstitial lung disease from that.
So you have to have a good model to be able to study in.

I think we have time for one and maybe two questions. So just my question come from pathology NGS, so this persistent cells. So when we get that tumor treated and recurrent, we see additional mutation in GFR amplification, some tumor exchange to become neuron decri and squamous. These persistent tumor cells where they are located in in these pathways clinically typically if we take.
one of these persistent cells and do NGS on them, they don’t have any other genetic alterations compared to the parental because they’re basically just rewired to be able to survive. And if you in that preclinical experiment if you take off the drug they regrow and they’re the signaling pathways look like look the same as they do in the parental cells. So it’s it’s it’s sort of an adapt, it would fall under sort of an adaptive resistance that allows survival but not necessarily driven by a specific genomic mechanism. OK,
00:57:21.440 --> 00:57:22.400 David, I think this will
be the last question from pathology.

00:57:25.760 --> 00:57:27.704 So the protein expression of
trope 2 and EGFR spans

00:57:29.912 --> 00:57:31.957 about a two log dynamic range.

00:57:33.745 --> 00:57:35.057 Have you ever looked at the levels

00:57:35.057 --> 00:57:36.560 of protein expression to correlate

00:57:36.560 --> 00:57:37.240 with your ADADC effects that you see?

00:57:37.240 --> 00:57:39.950 So clinically that’s been looked

00:57:39.950 --> 00:57:42.525 at and disappointingly has no

00:57:42.525 --> 00:57:45.000 correlation with the efficacy of

00:57:45.000 --> 00:57:47.440 trope 2AD CS or her three AD CS.

00:57:47.440 --> 00:57:50.080 Now maybe it’s because we don’t

00:57:50.080 --> 00:57:54.392 have the right assets to look at.

00:57:54.392 --> 00:57:56.784 Maybe it’s because other things you
you need the expression of the target, but you need other things. The antibody has to bind the target. It has to be internalized. It has to be transported to the right cell compartment where then the conjugate is cleaved and and then can kill the tumor cells. So maybe there are other things that are important in that in that overall efficacy as well not just the expression of the target. Great. Well possibly. Again, thank you so much for really a fantastic talk and for coming to visit. I will just make one announcement.
which is after this in the next couple minutes we're going to gather outside and and the fellows and other trainees are going to have a chance to ask you more questions and really look forward to that as well. Thank you again.