Real pleasure to introduce Roy Herbst.
Roy of course needs no introduction to all of you.
You can see his title on the screen Moving from Palliation to Cure Progress in the treatment of non small cell lung cancer.
But let me just make a couple of comments.
So Roy has really witnessed over the course of his 25 year career or so since completing training of has has witnessed a real revolution in lung cancer.
And I remember when I was a fellow and nobody was interested in lung cancer.
cancer and there seemed to be little hope for progress in lung cancer. And that has really changed so very dramatically. And as Roy has witnessed, he’s also participated in it and he has been involved in the vast majority of clinical trials that have led to major changes in lung cancer, whether that’s related to EGFR, associated lung cancer or for that matter, trials focused on immunotherapy and other treatments. So great pleasure to introduce Roy. He will take us through this talk and is a great inaugural speaker. Thank you, Eric.
And it’s great to be back here in person in the auditorium and happy Friday everyone. And what I’m going to do in the next 45 to 50 minutes is give you a little bit of a tour of lung cancer. So actually my journey began here at Yale 44 years ago and my Pecam professor’s in the front row, Don Engleman and it’s amazing to see you and I actually wasn’t his course like he would probably have probably been but it’s you know, Yale’s just a phenomenal place.
me to be to be here and I gave a grand rounds about 12 years ago when I first arrived. So a little bit of progress since then and I’ll show you that now my disclosures. So we’re back. This was last week at East Haven. We had our ASCO review and a dinner for some of the faculty. It was just great to see so many people there and the spirits there. We had a great day discussing all of our different divisions, both solid and liquid advances in the field and it’s good to see so many of those being done here at Yale.
And then of course we had many of our fellows and actually we're really multidisciplinary of course. We have our hospitals team was there, many of our fellows were there, we had surgeons there, we'd love to have our surgeons there, one thing that I want to get across today is the way we're making progress in lung cancer and many diseases. This is in a multi modality fashion and you know the burden of lung cancer is great. I think most of this group is aware of that.
but it’s the leading cause of cancer death worldwide. You know, more, more cases, probably a skin cancer diagnosed of course, but for you know, more, it’s more breast cancer in women and prostate cancer in men. But lung cancer is the number one killer with over 2 million deaths a year in the world with over 200,000 deaths in the United case, 200,000 new cases in the US with over 130,000 deaths. So this is the reason there’s so much research and pharmaceutical
development in this area.

84% of lung cancer is non-small cell lung cancer.

A great effort now still with small cell lung cancer used to be that was only associated with smokers.

It’s still mostly with smokers.

But now we know that EGFR mutated lung cancer can develop into small cell lung cancer and Sheng lives in the 2nd row sort of leads to that effort here and she’ll probably give a grand round.

Oh yeah,
thank you

and we'll hear from Ann hopefully in this series later this year. Well when I started out you know as after I left Yale and I spent some time in New York at Cornell and Rockefeller. I went up to Boston and I was working at Dana Farber and I said this last week at some of the fellows. I got the job in lung cancer because that’s all it was. You know the breast cancer jobs were all filled. The leukemia and lymphoma jobs actually liked lung cancer and was very interested in it. I had a wonderful mentor,
Emil Fry, also a Yale graduate, but it was pretty dismal and it’s very hard.

As oncologists to work in the clinic when you don’t have tools to offer.

We had tools of chemotherapy, but this is what survival curves look like about 25 years ago for lung cancer.

And you can see there’s really none at all.

You know, at two years.

There’s very little survival at three years.

Almost nothing.

And progression was quite steep and there was all this excitement about Dosi, Taxol, Packley, Taxol, Amcitabine.
Carboplatinum.

These drugs made a difference and they did improve survival, but to a very small extent. A median survival is of 7 to 8 months. So the question was a paradigm shift was needed. And you know, you’re really a product of your mentors. And I was very fortunate at Dana Farber, Tom Fry. In the later years of his career, I became his mentee and we met, you know, at least two or three times a week. And he always said take your best
00:05:31.057 --> 00:05:32.977 drugs and use them early use them you
00:05:32.977 --> 00:05:34.696 know in the multi modality setting
00:05:34.696 --> 00:05:36.700 with surgery with radiation and we
00:05:36.700 --> 00:05:38.537 already had seen that in lung cancer
00:05:38.537 --> 00:05:40.132 back in those days because chemo
00:05:40.132 --> 00:05:42.309 radiation it was a study done by
00:05:42.309 --> 00:05:44.627 Doctor Dillman back in the the late 80s,
00:05:44.630 --> 00:05:47.054 early 90s had shown that there was a
00:05:47.054 --> 00:05:49.235 benefit for chemo radiation in this
00:05:49.235 --> 00:05:51.503 disease and it did improve survival.
00:05:51.510 --> 00:05:53.750 So what causes lung cancer?
00:05:53.750 --> 00:05:55.374 I could give a whole talk on this
00:05:55.374 --> 00:05:56.763 and and tobacco cessation efforts
00:05:56.763 --> 00:05:58.611 that we’re we’re doing here and
00:05:58.611 --> 00:06:00.530 with the ACR and you know we have a

a large tobacco grant here at Yale

and that that’s very important for

our community cause New Haven is a

community where smoking is higher than

than in the rest of the United States.

But as I said many of the lung

cancers are non-smoking related now

and you can see actual mutations

so we can target those.

So we actually know driver mutations

so we can target those.

But there are now at least ten other

targetable alterations and we’re
NOTE Confidence: 0.61711353
00:06:30.260 --> 00:06:32.672 seeing evidence of benefit,
NOTE Confidence: 0.61711353
00:06:32.672 --> 00:06:33.538 you know,
NOTE Confidence: 0.7823865
00:06:33.540 --> 00:06:34.480 with a broad perspective.
NOTE Confidence: 0.7823865
00:06:34.480 --> 00:06:35.420 I can see it.
NOTE Confidence: 0.7823865
00:06:35.420 --> 00:06:36.500 Of course, to any given patient,
NOTE Confidence: 0.7823865
00:06:36.500 --> 00:06:38.180 it’s still not nearly enough.
NOTE Confidence: 0.7823865
00:06:38.180 --> 00:06:40.168 And I’m sure almost everyone here has
NOTE Confidence: 0.7823865
00:06:40.168 --> 00:06:41.780 some experience either as a physician,
NOTE Confidence: 0.7823865
00:06:41.780 --> 00:06:43.938 as a family member, as a friend,
NOTE Confidence: 0.7823865
00:06:43.938 --> 00:06:45.294 with someone who’s had lung cancer.
NOTE Confidence: 0.7823865
00:06:45.300 --> 00:06:47.500 And while we can see that in men
NOTE Confidence: 0.7823865
00:06:47.500 --> 00:06:49.237 survival death rates are coming down
NOTE Confidence: 0.7823865
00:06:49.237 --> 00:06:51.316 and in women with a little bit of
NOTE Confidence: 0.7823865
00:06:51.316 --> 00:06:53.708 a lag of smoking in women began
NOTE Confidence: 0.7823865
00:06:53.708 --> 00:06:55.834 later but still if you look in men
NOTE Confidence: 0.7823865
the incidence is coming down a lot of
that’s screening and smoking cessation
but the mortality is coming down even more.
And in in women the same 1.2 and 3.1.
So we are making a difference in these data.
You know the data you get from the American
Cancer Society is always two or three,
and four years old.
So I think this,
this shows some of the targeted therapies
which I’ll talk about in the first
half of the talk and the immunotherapy
benefits are are still on the horizon.
Well, we’ve built an outstanding program.
We’ve had retreats over the years.
This is a retreat about 5-6 years ago.
And I guess want to point out two things about this picture. One actually three things. One, this is a great group multidisciplinary working as a team. There’s myself that’s Dan Baffa, We held this at the Business School and David came in and inspired us with some of his you know go after the problem hard. He gave a very amazing speech. Of course David passed away or in the last few years, but then I also want to point.
out that’s Roy Decker.

We had one of the best radiation oncologists ever, both as a clinician, as a person in with patients and he passed away recently as well. So we lost a great member of our team. But I just wanted to just say we miss you dearly Roy.

And then you know we’ve continued to to meet, this is a few years later and you can see it’s a team. The only way we’re going to make progress is as a team, as a multi modality team and this is more of a clinical meeting.
I'll show you a translational meeting at the end. But you can see it's a team approach to lung cancer and you can see there's Dan Lynn Temui from pulmonary, and who unfortunately can't be here today, but she sent me a nice note and this was over at the West campus. Now the centers, you know these disease centers, I just say thought I'd say a few words about that. We talk about it a great deal.
That’s the goal.

Centers of excellence, multi modality centers of excellence, taking care of lung cancer throughout Connecticut throughout the network.

You know we have 15 sites around We we are going to have experts at all those sites seeing lung cancer. We might not have every discipline at each center, but we will work as a team to coordinate and really build a big tent, bring the science to the patients.

The only way to continue to make progress
and I hope you’ll see that at the end of my hour is by bringing science to the clinic. That’s the theme of today’s talk.

So we began the spore now a God, it’s hard to believe almost 10 years ago. We have three projects in the spore cyclic 15, which is and I’ll tell you a lot about that, that’s actually featured in the CCSG grant both in the DT and the immunology programs. And what you’ll it’s a new agent developed here at Yale and liping Shen’s lab. The mechanism based approach is to targeting EGFR are very relevant to
the first part of my talk and brain metastases which I’ll talk about as well.

And you can see we have Coors and and David and David’s in the front row.

We have wonderful bio statistical core, we have developmental programs and we were first funded in 2015.

So this effort began on March 1st, 2011.

When I arrived here we had a number of submissions just for anyone who is getting depressed.

It took three submissions to get this score and so it’s not easy but it’s been great and you’re gonna see and why in a moment.

And it was renewed in 2020 a lot more
easily and now we're gonna renew it again because I've taken on a new MPI and Doctor Paletti who's in the front row and 2nd row and working with Lee Ping who remains the Co Pi. We're going back in in January. So we wanted to wait till the core grant went in so we weren't competing for the same resources. Although there is I guess a site visit coming up too and the beautiful thing about the Spore is we have developmental projects over 50 of them over the years and you can see these are career enhancement program,
00:10:38.930 --> 00:10:40.210 you know young investigators
NOTE Confidence: 0.6782555
00:10:40.210 --> 00:10:41.810 who aren’t working lung cancer,
NOTE Confidence: 0.6782555
00:10:41.810 --> 00:10:43.476 we’re getting them involved in lung cancer
NOTE Confidence: 0.6782555
00:10:43.476 --> 00:10:45.687 and this is a developmental research program.
NOTE Confidence: 0.6782555
00:10:45.690 --> 00:10:47.650 We could have 10 projects on the SPORE.
NOTE Confidence: 0.6782555
00:10:47.650 --> 00:10:49.450 The problem is you can really only have
NOTE Confidence: 0.6782555
00:10:49.450 --> 00:10:50.814 three projects on these grants because
NOTE Confidence: 0.6782555
00:10:50.814 --> 00:10:52.410 the NCI continues to cut the funds.
NOTE Confidence: 0.6782555
00:10:52.410 --> 00:10:54.144 We have developmental funds and and
NOTE Confidence: 0.6782555
00:10:54.144 --> 00:10:56.369 and donor funds we used to enhance it.
NOTE Confidence: 0.6782555
00:10:56.370 --> 00:10:57.446 But look at this,
NOTE Confidence: 0.6782555
00:10:57.446 --> 00:10:58.522 all the different departments
NOTE Confidence: 0.6782555
00:10:58.522 --> 00:10:59.540 that are involved,
NOTE Confidence: 0.6782555
00:10:59.540 --> 00:11:00.760 it’s building a community of
NOTE Confidence: 0.6782555
00:11:00.760 --> 00:11:01.980 lung cancer here at Yale.
NOTE Confidence: 0.6782555
00:11:01.980 --> 00:11:06.180 And I think they’re about 17 or ones.
And this is the team.

And again, I just want to point out Anna Esteppe here, who now Ed Cafton, actually Julie Boyer many years ago was our initial administrative leader and then Ed Cafton for many years. Now of course he’s working closely on the CCSG but there’s Anna Esteppe are now staff who who just is doing a phenomenal job and actually made this slide for me. We probably need a second slide. These are all the people that are working.
in the community of lung Cancer Research.

And then I just want to give a little shout out to Katie.

So we had a little we went to New York last week and maybe two weeks ago now and Katie was honored by the Lung Cancer Research Foundation and see the multi modality in this Shen Liu of the Sheriff Pathology Valentina from genetics.

Some of us really, we’re a community that’s tackling this disease.

So now let’s do a little science.

I’ve already used 10 minutes up, but you know, I’m always taking pictures.

You see why.
So what about targeted therapy?

I'm going to tell you about targeted therapy, immunotherapy in the future.

And I might skip through some slides if it's going along.

So we have time for questions because you're here in person.

We should be interactive.

I began when I finished my work at Dana Farber.

I went to MD Anderson and I was telling one of the fellows yesterday.
00:12:16.844 --> 00:12:18.390 when I was meeting with her,
NOTE Confidence: 0.35788172
00:12:18.390 --> 00:12:19.625 it’s all about the mentors
NOTE Confidence: 0.35788172
00:12:19.625 --> 00:12:21.310 you have and I had worked,
NOTE Confidence: 0.35788172
00:12:21.310 --> 00:12:22.150 I had been at Yale,
NOTE Confidence: 0.35788172
00:12:22.150 --> 00:12:23.542 I had worked in Kim Darnell’s
NOTE Confidence: 0.35788172
00:12:23.542 --> 00:12:24.470 lab at at Rockefeller.
NOTE Confidence: 0.35788172
00:12:24.470 --> 00:12:25.922 I was very interested in signal
NOTE Confidence: 0.35788172
00:12:25.922 --> 00:12:27.211 transduction and I was very
NOTE Confidence: 0.35788172
00:12:27.211 --> 00:12:28.825 interested in EGFR and EGFR receptor.
NOTE Confidence: 0.35788172
00:12:28.830 --> 00:12:30.937 And just around that time the first
NOTE Confidence: 0.35788172
00:12:30.937 --> 00:12:32.221 small molecules and antibodies
NOTE Confidence: 0.35788172
00:12:32.221 --> 00:12:33.836 had been developed against EGFR
NOTE Confidence: 0.35788172
00:12:33.836 --> 00:12:35.824 and we knew that in epithelial
NOTE Confidence: 0.35788172
00:12:35.824 --> 00:12:37.424 tumors such as lung cancer,
NOTE Confidence: 0.35788172
00:12:37.430 --> 00:12:39.030 EGFR was up regulated.
NOTE Confidence: 0.35788172
00:12:39.030 --> 00:12:41.030 So I was very fortunate.
Juan Kihan, who is my mentor and who had recruited me to MD Anderson brought me upstairs to the president’s office.

John Mendelson, who had worked in the e.g. field and these new molecules were coming through and they offered me the project and I just said sure. And I, I don’t think I realized how good it was at that time. I knew that it was a good science and the science was evolving and then we started to do clinical trials.
But also we worked in the lab to try to identify biomarkers and I went to start my first clinical trial and a drug called ZD 1839 and the investigator meeting was in Palm Beach, FL which is nice. My parents live there and then I go to the hotel and who’s sitting across from me but Pat Larusso that’s when I met Pat in 1997 and we started and we were the Co leaders of this first trial of ZD 1839, which became known as confitinib and some might know it as Aressa. And we started using this drug, an oral agent against patients with
lung cancer, with what we would call broncholoviral lung cancer. And in one of 10 patients we saw this, this clearing unheard of. You saw the survival curves I showed you. And these would be patients who could hardly walk into the clinic and then a week or two later they’d be feeling great. We didn’t know at that time what the biomarkers were. We thought it was easy of our expression. Of course, mutations were found after about 1002 thousand patients were treated and and people looked back.
I'll show you that in a moment.

We knew that it was women were more likely to respond than men,

but it was really people who had smoked less and smoking.

You know, if you smoke, you're more likely to have other mutations like K Ras.

And the never smokers did well,

we did a lot of skin biopsies.

That's that's when I first met Pat

because we were talking at the meeting about doing skin biopsies and I said,

at MD Anderson at the time and I said, oh,

I need to bring in my dermatologist
and we need to do a contract and Pat just gets up and says I do them myself and then sew them up. It was like pretty. She was pretty intimidating and and and now you know why she’s been so successful. She does it herself. Well, then of course skipping a little ahead because it’s only an hour talk about four years later, five years later. And John Mendelson and I used to always talk about that. How can we keep it?
Actually it was eight years later, the mutations were discovered.
How can we do this more quickly?
That’s why with all the work we’re doing with pathology and biomarkers,
we’ve got to be even quicker now.
Sequencing techniques were still developing.
You know, it wasn’t long before this.
We’re just doing the Max and Gilbert sequencing and reading the gels, right.
So but, but a couple of centers,
Boston and New York took the samples from patients who were getting these drugs.
These drugs went to what we call...
00:15:02.226 --> 00:15:03.395 an extended access trial.
00:15:03.395 --> 00:15:05.777 People could get it off label while
00:15:05.777 --> 00:15:07.086 that while we were waiting for the
00:15:07.086 --> 00:15:08.578 drugs to be approved and many patients
00:15:08.578 --> 00:15:10.068 were treated and of course it was
00:15:10.068 --> 00:15:11.190 found that in the EGFR receptor,
00:15:11.190 --> 00:15:12.226 which of course would be a dimer.
00:15:12.230 --> 00:15:13.695 This is a simplification in
00:15:13.695 --> 00:15:14.867 the tyrosine kinase domain.
00:15:14.870 --> 00:15:17.000 There were specific mutations mostly at
00:15:17.000 --> 00:15:19.437 that time discovered in exxons 19 and 21.
00:15:19.440 --> 00:15:21.078 Now we see them in Exxon 20 as well.
00:15:21.080 --> 00:15:22.922 And these mutations of course activated
00:15:22.922 --> 00:15:24.838 and caused this to be a driver.
00:15:24.840 --> 00:15:26.574 And then these small molecules bound
into the ATP binding site and we’re very potent.

They had some rash,

they had some diarrhea,

but they were very potent.

And that led to this is actually being in a place like MD Anderson patients just flowed in and we had a big phase one clinic.

I think we must have treated a couple 100 patients in the first two or three years and I LED the trial and that’s Cicely Harris.

She was one of the first patients.

And, you know, she was written up in the Wall Street Journal because the idea was we probably didn’t.

We didn’t cure her lung cancer.
She only lived for nine years, but we prolonged her survival with good quality of life. And that’s why Tara Parker Pope, you know, wrote this article about her. It’s like insulin for diabetes or hypertensive medicine. But that’s the problem. And it continues to be the problem with EGFR mutated lung cancer. I’ve been doing this for 25 plus years. No one’s unfortunately in the advanced stage ever cured. That’s why the work that Katie and her lab are doing.
Mark Lemon, I’ll show you the project.

We have to find new agents because we have to always stay one step ahead.

These are the first generation drugs gafitinib and orlatinib. This was known as OSI 774. For those interested, this was actually a Pfizer drug and Pfizer when they merged, and Pfizer when they merged, when they took over the Pharmacia drug, they they went with the Pharmacia product and made a bit of a mistake because this drugs actually became the number one ETFR inhibitor. These are, these are reversible inhibitors.
They’re non specific for mutated cells that get both wild type and mutated cells.

Then there was a second generation drug, a fat nib, which also blocked her two and her four.

You add more TKI activity, you get more toxicity.

We actually did a big trial of this with cetuximab showed some increased activity but not enough.

And then of course the the third generation drug asimertinib which is an irreversible inhibitor which has good brain penetration and it’s easier for our mutation specific.
So they'll there's less rash and diarrhea. It can be given to patients for longer periods of time without toxicity and that's how we were able to move this drug to the earlier stage. And this is just an example and again I'm just giving you a bit of an overview today, but the most common mutation for resistance is known as T790M and the patients that have that this drug lasimertinib you know was first studied to target that resistance mutation which is about 50% of the resistance and you can see the activity that was seen there over 6070% response.
And this quickly became the front line agent again bring your best drugs to the front line. But again few if any are cured. That’s the problem. That’s what I’m gonna talk to you about now I was at MD Anderson and you know when you know about now we’re putting about 100 and 10120 patients on lung trials with three or 400 patients on trial. But what I noticed I was leading the group lung group there we’re doing it on 20 different trials.
So we said can we do one trial and use biomarkers to decide who should get which drug. It really is a sociology project and we didn’t have a sociology department like we have here or psychology. But what we did is we actually convinced the team that it would be better for all of us to work together on one trial and we used a little bit of push and pull because the science was exciting and at that time...
and David Meta who’s here now, and I work with him at that time we could get biopsies. Core biopsies, prior to 2004, most lung cancer biopsies were fine needle aspirations. You had a little bit of few cells, maybe you made a cell block, but you didn’t have really enough tissue for sequencing. But now that sequencing was coming to bear. We said can we do a trial called Battle and we worked with a pathologist, Ignacio Astuba Jack Lee,
a biostatistician,

Ed Kim now at City of Hope and

with our mentor Wang Ki Han.

We developed a trial we called Battle

and what we called it is biomarker

integrated approach of targeted

therapy for lung cancer elimination.

So what we did is we had four

or five different drugs.

We did a biopsy.

We got the result within 14 days

and then we used that result to say

this patient has an EGFR mutation,

they should go on heratinib.

This patient has a VEGF up regulation,

they should go on VET detonib and
I actually think it’s and we used an adaptive statistical design and I’ve talked about that here before. The results did pan out. We, we found new biomarkers for VEGF inhibitors. The EGFR mutation came out of the story. Now of course you say we knew that already, but we didn’t. This was before the mutation was fully validated and we showed that core biopsies were feasible and and safe. And this is about when I came to Yale. So when I came to Yale, I said let’s let’s do a battle trial here.
And David RIM, my friend in the front row and that’s Jeff Sklar. I miss good old Jeff.

You know, he used to always be in the front row at the grand rounds he’d be here and I said can we do a core biopsies? I was saying I should go back home and then that was Rocco who was working with us from the CTO. And that’s Julie Boyer, that’s Emily who now works as an APRN. She was a researcher nurse at the time.
We put a little team together and we ended up putting about 40 or 50 patients on the battle trial. Now it wasn’t as many as 300 MD Anderson but we started doing a tissue based approach and and that’s how that was actually funded by an RO one that I brought with me from Anderson. But moving to the what I want to tell you about it in my first story is how can we do better in lung cancer. We’re not going to do better by
using these targeted therapies just in advanced disease.

We have to find the disease earlier and we're finding disease early because of screening and because of smoking prevention and at the time that someone comes in for smoking prevention that’s a teachable moment. But we know that even in lung cancer when you find it early you know and so often they find it in the emergency room these days, right they’re doing a cardiac scan or some other scan. Someone has a small nodule, the five year old survival even
even there is only 60 to 74% that’s how metastatic lung cancer is. And if it’s stage 2 with a few other nodes, 47 to 55% and it happens to be stage 3 with N2 lymph nodes or stage 3 B 38% five year survival. So even early disease even with chemotherapy is not as curable as we would like. So if someone has an EGFR mutation which are about 1015% of the patients in the Western world and as many as 40% in the East, Asia, China, wouldn’t it be nice if we could and we know that the percentage
of mutations are about the same across the spectrum of stages.

Wouldn’t it be nice if we could give the EGFR inhibitor earlier.

So that’s that we sat down about 10 years ago now a group of us and I had a colleague Masa Hara Suboi from Japan and Ylan Wu from China working with AstraZeneca.

We said let’s let’s design this trial now and they were very proactive and and they said, let’s do it because they knew an active and trial would take a long time.

So that’s the Adura trial and the idea
was to take patients who had been completely resected for lung cancer and you can see the eligibility here. And then we stratified them by their stage 1B2 or 3A, they all had R0 resections, meaning all the tumor was removed with clean margins. We only took the two most canonical EGFR mutations, 19 and 21, and we did stratify by race. About 2/3 of these patients were Asia. You can imagine it. There were more of these mutations in Asia, so more patients went on there and
then the patients were randomized to
firstly they could get chemotherapy
if it was deemed appropriate.
Most of this takes two and three lung cancers, get chemotherapy, platinum based chemotherapy and it’s about a 5 to 6% improvement in survival. Not a lot but it does improve survival.
I would use it because it’s something but then we randomized to either acimertinib at 80 milligrams once a day or placebo. at 80 milligrams once a day or placebo. I’m often criticized how could you do a placebo, but there were no data. There were plenty of trials before this that had tried other EKFR inhibitors and looked in this setting and nothing worked.
They’re all too toxic.

But we figured this drug was brain penetrant, it was EKFR mutation specific, it could be used and it would be safely administered.

So we used OSTEO Mertini versus placebo and we treated for three years.

But the primary endpoint of this trial was disease free survival, no disease recurring. Remember they started with no disease.

So we’re seeing if anything recurs and the trial was powered for a hazard ratio of .7, meaning a 30% improvement.

So about I guess it’s almost four
years ago now in April there was a safety review of the trial going on. We no efficacy but the cure of that safety committee. I don’t know if anyone here has ever been on a safety committee. He said something’s wrong here. It looks like one of the groups is doing better than the other and normally it’s the control group is doing better and they stop the trial but they actually looked at it and said the the treatment group is doing so much better, it’s unethical to keep the trial going. So,
so we actually got a call it was in April.

We looked at the data and and actually the hazard ratio I’ll show you in a moment was so good that you’ll see where things went after that.

So this was depending on your religion, Good Friday and Passover, it was Good Friday and Passover, I’ll go with Passover,

but you can see here, here it was in that year the stakes 1B and 3A patients here are patients who got the acid mertinib in the adjuvant setting and here is the control and the hazard ratio.
was .2 or an 80% improvement.

So that was phenomenal, better than expected.

Of course, you would expect that this would work, but with this sort of separation and this sort of result and it actually made a plenary talk at ASCO that year and then we’ve updated it just earlier this year.

This is the, this is actually the review at the time when it would have normally been analyzed and it’s still been analyzed and it’s still .27 or 73% improvement.

So using a drug early keeps the disease...
00:24:39.303 --> 00:24:41.560 Now where do you think the disease is kept from recurring from?

00:24:41.560 --> 00:24:43.580 Well, the first, I guess we'll show you all parameters benefited sex, age, whether or not the patient was a prior smoker, Asian or non Asian, all three stages, both mutations.

00:24:49.800 --> 00:24:51.452 So you always do better with XN 19 deletion, it's a loss of it's a deletion versus the point mutation which can revert a bit easier and you can see whether or not the patient got adjuvant chemotherapy.

00:24:51.452 --> 00:24:53.896 When you look at a forest pot like that, for those who aren't used to it, anything to the left of 1 is good.

00:24:53.896 --> 00:25:01.299 So you always do better with XN 19 deletion, it's a loss of it's a deletion versus the point mutation which can revert a bit easier and you can see whether or not the patient got adjuvant chemotherapy.

00:25:01.299 --> 00:25:03.283 When you look at a forest pot like that, for those who aren’t used to it, anything to the left of 1 is good.

00:25:03.283 --> 00:25:04.638 When you look at a forest pot like that, for those who aren’t used to it, anything to the left of 1 is good.
And then if you look what happened is in the patients who got out to Mercenib, you can see actually let’s start here, here the patients got placebo 46% who recurred. You can see that many of those are distant recurrences. Whereas in the small number of patients in the early data who who recurred on the ASA emergent drug only about half as many were distant. The drug is keeping patients from getting distant metastases. That’s what causes patients to die metastases to other organs,
brain, liver and bone.
And actually we looked at that and this is pretty phenomenal.
This is looking at the brain as the first site of recurrence, which is a major issue.
If you ask a patient with lung cancer, he or she will tell you I’m worried about my brain.
We just had AEAB for our spore last Monday.
That’s exactly what our patient advocate told us.
But you can see here’s patients adjuvant disease who got last Emergenib.
Here’s the control group hazard.
ratio for recurrence in the brain meaning a 76% decrease in the first recurrence being in the brain.

So it’s keeping the tumor from the brain. We’ll do this forever probably not but it did it for a long period of time. We treated for three years and here you can see now everyone was sceptical you know I don’t I never used to do the Twitter. Then I started doing the Twitter because people said you have to read the Twitter because people are being critical of your data. And now I don’t know how to do Twitter because it’s called X and
I haven’t figured that out yet but there were all these people that said well there’s no survival benefit. Now the drug got approved based on disease free survival, but there hadn’t been a survival benefit and we had to wait for a number of years to have 20% of the patients unfortunately die because that was the end point that had been pre specified to look at survival and it’s API you hate for that to happen you know because I’d rather there never be an end point because you don’t want anyone to succumb.
to their disease.

But I got a call last November that the trial was nearing the end and it was very interesting because Eric was the ASCO President. I'm thinking well this could be an ASCO presentation. So we're waiting for the data to make sure over the winter and then about March saw this curve and this is the survival curve and again it was a very big DFS benefit.

But in survival the hazard ratio is .49.

So here's the patients who got
osteomertinib and here's the control and you can see at five years, 88% versus 78%, so 10% improvement in survival, the hazard ratio .49, so a 51% improvement in survival. And remember the drug stopped here at three years. We only treated for three years. So now we have to continue to watch these patients. We have liquid biopsy samples. Hopefully next year I'll give another grand rounds. I have those samples.
I’m analyzing them now, but we’re not ready to talk about them unfortunately yet. And then it was pretty cool. So who knew that Eric was going to be the director here? It’s just like, it’s almost like an amazing coincidence. He’s the ASCO president and there I am presenting it to the plenary beside him and Kimi Ying. It was really cool. And you little can’t make this stuff up. It just sort of happened, right Eric, it’s who would have known? So it was really, that was phenomenal.
I was pretty nervous.
The only best thing about, best thing about the plenary is the green room, the drinks and the food in there. Phenomenal. See, that's the secret of the ASCO.
Now you see the overall survival both if patients got actually in chemotherapy or without actually in chemotherapy. So you give it if you know sometimes patients don't want it and there's a big push now to avoid the
chemotherapy we’re looking at that. But right now we suggest that patients get chemotherapy if they can. And then you know the big critique of this trial and for those that read the New England Journal, there’s a letter I responded to a letter today from an investigator in Italy who said well you didn’t not all your patients got ostomertinib. So it’s not really a fair trial and they’re right. Not everyone could get ostomertinib. But look in the ostomertinib
group and in the placebo group about 80% to 90% got an EGFR inhibitor in a second line setting did only 43% got osthomordinib. But the drug wasn’t even improved in the front line setting when we started the trial. So well it’s not perfect, patients have done better if they got an osteomordinib early probably. But I I would what we said in this reply is the difference is so great. I think use your best drugs earlier and I think this these data hold hold water and
then you know it’s not without toxicity.

Be careful as physicians, as nurses, as caregivers, you know,
it’s easy for you to say there’s no problem
when you’re giving a drug versus a placebo,
there’s always going to be added toxicity and this drug does cause some
diarrhea and it does cause some diarrhea
there’s always going to be added
toxic and this drug does cause some
rack and it does cause some diarrhea
there’s always going to be added
toxic and this drug does cause some
rack and it does cause some diarrhea
there’s always going to be added
toxic and this drug does cause some
rack and it does cause some diarrhea
there’s always going to be added
toxic and this drug does cause some
rack and it does cause some diarrhea

and it is debilitating for patients in,
in about 4 to 5% of the cases.
We have to be sensitive to that.
Some patients need breaks,
some need dose reductions.
But for the most part, if you look
at discontinuations and serious AE,
there were 14% on placebo versus 20%
00:29:45.090 --> 00:29:47.169 on the drug which is pretty low.
00:29:47.170 --> 00:29:48.871 But again there is toxicity and this
00:29:48.871 --> 00:29:50.939 is where quality of life and you know
00:29:50.939 --> 00:29:52.224 the survivorship clinic and others,
00:29:52.230 --> 00:29:53.902 you know we need to look at this
00:29:53.902 --> 00:29:54.830 and help patients.
00:29:54.830 --> 00:29:57.070 So what’s in the future,
00:29:57.070 --> 00:30:00.541 we’re continuing to file the overall
00:30:00.541 --> 00:30:02.109 survival because what’s going to
00:30:02.110 --> 00:30:03.595 happen in five years and 10 years,
00:30:03.595 --> 00:30:04.189 we’re doing a bunch of
00:30:04.190 --> 00:30:06.926 We’re going to have Pasayani here for the
00:30:06.926 --> 00:30:08.790 Calabrese lecture this year and he’s going
00:30:08.790 --> 00:30:10.190 to tell us about procester Tri cells,
which he studies and Katie

There are still cells that remain resistant to EGFR inhibitors.

We actually have blood from about 1/3 of the patients.

It’s very hard to get samples out of China, but from the Western world and from Japan, we do have blood samples and tissue samples.

So we’re looking at that.

We’re also looking at, you know, there are trials looking at neoactuvent osteomerotradium.

Now that’s all the rage right now.

We’re looking at earlier disease.

Adura 2 is looking at this
00:30:38.510 --> 00:30:39.670 was stage 1B disease,
NOTE Confidence: 0.29164207
00:30:39.670 --> 00:30:41.110 so more than 3 centimeters.
NOTE Confidence: 0.29164207
00:30:41.110 --> 00:30:42.014 Everyone always calls me
NOTE Confidence: 0.29164207
00:30:42.014 --> 00:30:43.144 what about the small tumors,
NOTE Confidence: 0.29164207
00:30:43.150 --> 00:30:44.788 I think it'll probably work there too.
NOTE Confidence: 0.29164207
00:30:44.790 --> 00:30:45.982 But we need to do the trial and
NOTE Confidence: 0.29164207
00:30:45.982 --> 00:30:46.967 we're actually doing a trial where
NOTE Confidence: 0.29164207
00:30:46.967 --> 00:30:48.147 we're giving the drug for five more
NOTE Confidence: 0.29164207
00:30:48.147 --> 00:30:49.161 years because there is some sense
NOTE Confidence: 0.29164207
00:30:49.161 --> 00:30:50.990 when you stop the drug that the the
NOTE Confidence: 0.29164207
00:30:50.990 --> 00:30:52.310 brain metastasis started to increase.
NOTE Confidence: 0.29164207
00:30:52.310 --> 00:30:53.690 So there might be some patients
NOTE Confidence: 0.29164207
00:30:53.690 --> 00:30:55.190 who are cured in my opinion,
NOTE Confidence: 0.29164207
00:30:55.190 --> 00:30:57.381 but some who are just having cytostatic
NOTE Confidence: 0.29164207
00:30:57.381 --> 00:30:58.935 stability of disease and that’s
NOTE Confidence: 0.29164207
something we have to figure out.

So I’ll just end this portion of the talk with this slide.

So another mentor of mine, I don’t know if anyone knew Josh Fiddler,

but I I, I actually when I was at MD Anderson, I had a small lab with him and and Josh

used to always say metastases are are what would kill patients and he talked about the metastasis cascade.

So I think what we’ve really shown here is we’ve taken our best surgery and chemotherapy and we’ve added targeted therapy to keep patients from progressing in the brain,
liver and bone.

And I think this is a paradigm now we're going to see more of the drug was approved as I said in 2020. There are a whole host of other mutations. As I mentioned, there's a trial called Alina that will be in the news in two weeks from today, you'll hear about Alina, this is electinib, it's the Roche drug for ALC. And we, we have a press release that that trial is positive for disease, for disease free survival. And I bet they're not going to say wait for overall survival.
I think based on the Adura results, actually Anne and I are going to the American Medical Association next week for clinical trials meeting and I think at that meeting we're going to discuss this trial because as a paradigm. Disease free survival works. OK. And here's a little plug for Katie. And there's a little plug for Katie. But Katie and and Sarah and Mark, what an amazing team, Mark's a little younger there.
So here, here’s the group, I’m, I’m a little older so here’s the group that that’s been meeting and you know Mark’s now the Chief of Pharmacology and super duper team obtaining samples. We’re banking the samples, we’re looking at these samples that’s how science is going to be made and understanding resistance. And then we also have a project three of.
the spore looking at brain metastases.

I'm just putting a little plug in for that project.

No time to talk about it today.

And then we oh, this is important.

We have an alliance with AstraZeneca.

This has been critical for the sport because by developing industry alliances and this is one of the things I've been working on with the Dean's office in the last year and a half and I'm really enjoying it, working very closely with MENA Wang, who's pictured down here.

And here's Kathy Lynch from Yale Ventures. There's Pat.
We, we, we,
we started this together about 5-7 years ago. Here we are in Cambridge 2017 and
we all look the same and and
you can see that this this is just
an amazing collaboration because
that’s how we’re really making
difference and I got to move on but
this this is the timeline of that
alliance and here’s the most recent
visit actually Dean Brown was with us.
We’re really getting
funds but we’re getting drugs
and compounds test compounds.
Marcus I see in the front row.
I know he’s very excited about this. It really is the way we’re bringing this in and we’re expanding this now to head and neck cancers. We’re heading to breast cancer and other other cancers in the future. So this is going to be something that’s with AstraZeneca and other companies that will, I think be very important. So just in the last 20 minutes, a little bit about immunotherapy. That’s also an amazing new paradigm in lung cancer targeting immunotherapy and of course the checkpoint inhibitors. You know, the first trials
were done here at Yale.

I don’t know if everyone realizes that.

And of course, we have Lee Ping Chen here.

There’s a very nice article about

him in fierce Biotech yesterday

talking about his contribution to the

development and discovery of PDL 1.

So this is the probably the

first responder in lung cancer.

I don’t know if Scott.

Scott’s probably in clinic now

because that’s why he sees so many

patients and helps so many people.

So this is a patient Maureen

who came to Yale Squamous lung
cancer wasn’t a candidate for any of those targeted therapies, 3 times refractory lung cancer. And June 2010 she went on the trial of MDX one, one of that Mario was running with Scott and Harriet and you can see these large tumors in her lung and her liver. Within months they responded. The trial was for two years of what we now know as novolumab. Here she is a year 8, but her X-rays look this way. Now she comes back. We’ve seen her. I’m sure Tara’s seen her at some
NOTE Confidence: 0.71490145
00:34:52.244 --> 00:34:53.190 of the survivor events.
NOTE Confidence: 0.71490145
00:34:53.190 --> 00:34:55.134 This is the promise of a phase one
NOTE Confidence: 0.71490145
00:34:55.134 --> 00:34:56.869 trial of new drug development.
NOTE Confidence: 0.71490145
00:34:56.870 --> 00:34:59.586 The problem is this is only 15%
NOTE Confidence: 0.71490145
00:34:59.590 --> 00:35:00.646 but for This is why everyone
NOTE Confidence: 0.71490145
00:35:00.646 --> 00:35:01.830 wants to work in this field.
NOTE Confidence: 0.71490145
00:35:01.830 --> 00:35:03.310 We see a light at the end of the tunnel.
NOTE Confidence: 0.71490145
00:35:03.310 --> 00:35:04.750 It’s just a very long tunnel,
NOTE Confidence: 0.71490145
00:35:04.750 --> 00:35:06.416 but we know that 15% of patients
NOTE Confidence: 0.71490145
00:35:06.416 --> 00:35:07.748 are going to benefit.
NOTE Confidence: 0.71490145
00:35:07.750 --> 00:35:11.060 And then Scott and he he ran
NOTE Confidence: 0.71490145
00:35:11.060 --> 00:35:12.560 this trial OO 3:00 and basically
NOTE Confidence: 0.71490145
00:35:12.560 --> 00:35:14.086 this is an actuarial survival
NOTE Confidence: 0.71490145
00:35:14.086 --> 00:35:15.910 curve because it’s now with more
NOTE Confidence: 0.71490145
00:35:15.963 --> 00:35:17.505 than five years of follow up.
NOTE Confidence: 0.71490145
He published this in JCO in 2018 at

five years in the refractory setting on

the volnab 16% of patients are alive.

And when I use this slide to teach

in my clinical trials course,

I talk about the tail of the curve

because this is a non proportional hazards.

You have two slopes, 1 here,

You have two slopes, 1 here.

We know that there’s a tail problem is

how do we get more people off the tail.

These patients have primary resistance.

There are other things going on.

Maybe it’s another checkpoint,

maybe it’s a regulatory T cell.

This is why we shouldn’t just
study the next PD1 inhibitor

or the next PDL 1 inhibitor.

We need to think about what’s going on in the micro environment and

I’ll show you how we’re doing that.

So just quickly keynote one, Paul.

ADA ran this trial here at Yale a decade ago.

It was Melanoma lung cancer,

small cell lung cancer.

This was with Keytruda with

tembrelizumab that led to a trial

that I LED called KEYNOTE 10,

which established PDL 1 as a biomarker.

If you have high levels of PDL one,

you do better than if you have lower levels.
That led to using the pembrolizumab in the frontline setting and then that led to accurate therapy. Sarah Goldberg and Harriet working with Veronica Shang, they did the first study and this is when we’re saying we can get this study. We got this still plan on in three months and we’re getting back to that. They did a study where investigator initiated study where they took pembrolizumab because we’re already working with Merck and they did it in and we’re still getting data from this. And we took patients with small brain meds,
they had to be less than two centimeters
and we treated those patients with, with,
with the drug without any radiation.
If someone’s going to live for 2-3 years,
the one year survival with pembrolizumab
and a high PDL one patient is 35%.
So if you’re going to be alive,
actually the five year survival is 35%.
excuse me.
So if you’re going to be alive in five years,
you’d rather be alive without any
cognitive impairment from radiation.
So this was really established in this
trial that was both a collaboration
between Melanoma and the lung cancer
group and you can see here’s extra cerebral response and brain response and you can see they’re about equal.

And Harriet, it won’t tell you this, but I’ll tell you this and it wasn’t the New York Times. So I’m not reaching any confidentiality. But when a 99 year old ex president had Melanoma in the brain about eight years ago, they called us at Yale. And while Curran asked what are you doing with pembrolizumab in that setting? And you can, you can put the pieces together yourself. So what about precision medicine? How can that help?
Well, David RIM, I was asked to be the discussion at ASCO about six years ago for the early studies on the Volumab. So I went to my good friend David, who by the way used to work on breast cancer and he moved over to lung cancer and now Eric’s getting him back. The very pathologists are your pathologists, your statisticians, He works on the head and export too. The very the pathologists are your your your statisticians.
00:37:58.590 --> 00:38:00.030 critical core members.
NOTE Confidence: 0.2752451

00:38:00.030 --> 00:38:00.830 For any of these grants,
NOTE Confidence: 0.2752451

00:38:00.830 --> 00:38:02.195 you’ve got to have a good course
NOTE Confidence: 0.2752451

00:38:02.195 --> 00:38:03.560 and that we always get exceptional
NOTE Confidence: 0.2752451

00:38:03.560 --> 00:38:05.024 thanks to David and Kurt and
NOTE Confidence: 0.2752451

00:38:05.024 --> 00:38:06.467 now Sonia’s working with them.
NOTE Confidence: 0.2752451

00:38:06.470 --> 00:38:07.970 So you can see, I said, David,
NOTE Confidence: 0.2752451

00:38:07.970 --> 00:38:10.070 why is this PDL one marker so,
NOTE Confidence: 0.2752451

00:38:10.070 --> 00:38:11.753 so bad And Li Ping was with us and
NOTE Confidence: 0.2752451

00:38:11.753 --> 00:38:13.670 Li Ping said of course it’s not bad.
NOTE Confidence: 0.2752451

00:38:13.670 --> 00:38:14.720 I discovered it.
NOTE Confidence: 0.2752451

00:38:14.720 --> 00:38:17.835 but you just don’t measure it properly.
NOTE Confidence: 0.2752451

00:38:17.840 --> 00:38:19.720 And then David made this slide for me
NOTE Confidence: 0.2752451

00:38:19.720 --> 00:38:21.280 that everyone’s now used and and I
NOTE Confidence: 0.2752451

00:38:21.280 --> 00:38:22.918 make sure the credit was there David.
So everyone uses this and and
David has done very well at meetings and and and
Here’s one piece of lung cancer, one tissue piece and two different areas.
One area is stone cold negative for PDL, one for two different antibodies and one area is positive with two different results, you know slightly different and it matters where you measure it. The green is cytokeratin, so that’s tumor. The blue, the Dappy is the nuclei and that and you can see the red is PDL one.
It could be either in the tumor or the stroma. So it’s the variability of measurement and the sensitivity asset. But you gotta have PDL ONE for PD1 and PDL 1 blockers to work. And we have, we’re so fortunate. That’s why we got to make sure the freezers are backed up in our office. And we also have to make sure we have more liquid nitrogen because these samples are so valuable for the last decade,
the lung group has been collecting samples when someone comes in and they have recurrent disease and they’ve putting a little plug in for the.

When someone comes in and they have recurrent disease, we actually get consent to get their old biopsy.

And then when we get the new biopsy, the biopsy’s done with the help of the team.

And there’s Anna and Heather works with her sometimes goopang.

I don’t know if he’s here or maybe he’s online.

The team gets a fresh biopsy and we
get fresh tissue and we get paraffin,

we make transgenic, we make,

we make PDX mice. This is, this is.

And zenta or pathologist is usually

to make sure we get good tissue.

This is the key,

having samples from refractory patients.

We started this with TKIS,

but then we did this with IO agents.

We went and have the spore 10 years

there if we didn’t have this data set.

And we’ve used this both with our

own samples and with industry.

This is a very nice trial that

Scott and I and others did with

the drug known as MDX 1107.
Now it’s known as pembrolizumab.

So this was a phase one trial which we led here at Yale and it actually was published in Nature almost a decade ago.

But in this trial, we had patients with lung cancer who responded to a PDL 1 inhibitor.

But because we could get those fresh biopsies, we had pre and post biopsies.

So here’s a prebiopsy on this responding patient and you can see CD 8 positive T cells and then post you can see a lot more.

This is what you call the adaptive immune response.
This is, this is the blocking the PD1 PDL one up regulation of interferon

T cells coming to the tumor and then using an RNA chip.

And why did this? Why did we get this trial? Ira Melman, good old Ira Melman had moved to Genentech and I went out and had dinner with him. I knew Ira and Ira helped us to get this trial and with IRA’s group did this work for us the
RNA shift and you can see pre and post green is pre yellow is post. You can see this is an example of what’s happening when the immune response is active. So we understand what the active immune response is how is how do we get this to go on in every patient? 20% of patients responded in that trial but the other 80% did not and those patients that did not we described in this paper the immune desert you know CD 8 before and after the tumor just laughs at, at the PDL 1 inhibitor nothing happens.
00:41:26.738 --> 00:41:28.663 or you can have a non functional
NOTE Confidence: 0.6175327
00:41:28.663 --> 00:41:30.367 immune response where you have some
NOTE Confidence: 0.6175327
00:41:30.423 --> 00:41:32.263 CD8 cells and maybe a few more posts.
NOTE Confidence: 0.6175327
00:41:32.270 --> 00:41:33.712 But if you look at that immune
NOTE Confidence: 0.6175327
00:41:33.712 --> 00:41:35.054 shift completely flat and then this
NOTE Confidence: 0.6175327
00:41:35.054 --> 00:41:36.184 is actually something we’re seeing
NOTE Confidence: 0.6175327
00:41:36.184 --> 00:41:37.701 more and more of and I don’t have
NOTE Confidence: 0.6175327
00:41:37.701 --> 00:41:39.282 time to talk about it today but our
NOTE Confidence: 0.6175327
00:41:39.282 --> 00:41:40.931 next trial on the sport is going
NOTE Confidence: 0.6175327
00:41:40.931 --> 00:41:42.709 to target this that that the cells
NOTE Confidence: 0.6175327
00:41:42.709 --> 00:41:44.375 that get inhibited that can’t get
NOTE Confidence: 0.6175327
00:41:44.375 --> 00:41:46.339 to the tumor because you get this
NOTE Confidence: 0.6175327
00:41:46.339 --> 00:41:48.193 line of interference and we call
NOTE Confidence: 0.6175327
00:41:48.193 --> 00:41:50.550 this the the immune excluded cells.
NOTE Confidence: 0.6175327
00:41:50.550 --> 00:41:52.200 So more to come on this,
NOTE Confidence: 0.6175327
00:41:52.200 --> 00:41:56.040 I’m going to skip this for the sake of time.
We just have to do a little editing. So I will just say that now all these agents are moving up up front. We’re now in the process of taking immune therapies that are being used in the neo accurate setting. And it’s actually a very fertile time because when we sit at the tumor board, we have to decide are we going to do surgery and accurate therapy like I showed you for TKI inhibitor. So we’re going to use the neoactivant therapy 1st and we’re seeing about 15% half CR rate and a 30 to 40% minor CR rate, excuse me.
when we use these agents upfront. So that’s going to be the next stage neoactivant trials and I just want to make a plug for tumor boards. This is sort of what our tumor boards look like lately. So I would just like to as long as I have the podium today encourage people to go to tumor board and start having our tumor boards hybrid. We can’t have them all in person because we’re 15 sites. But the tumor board discussions are going to be really critical. These are drugs that were approved from Yale LED studies very proud of that.
All these drugs had some of their first studies here at Yale in the lung program and we have many more to come and we’re seeing that in all of our programs and that’s our experimental Therapeutics or DT. We can do the science on these studies. We understood the target brought it earlier to have the greatest advantage and we used targeted therapy.
00:43:29.126 --> 00:43:33.010 I told you about the the biobank we have.
NOTE Confidence: 0.27132082
00:43:33.010 --> 00:43:35.210 Well let me show you how it has paid off.
NOTE Confidence: 0.27132082
00:43:35.210 --> 00:43:36.995 So here we had patients who had
NOTE Confidence: 0.27132082
00:43:36.995 --> 00:43:38.387 immune therapy and they responded
NOTE Confidence: 0.27132082
00:43:38.387 --> 00:43:40.389 and then they had more immune therapy
NOTE Confidence: 0.27132082
00:43:40.389 --> 00:43:41.848 and they became resistant.
NOTE Confidence: 0.27132082
00:43:41.850 --> 00:43:43.890 So thanks to that poor protocol that we've
NOTE Confidence: 0.27132082
00:43:43.890 --> 00:43:45.768 had running for I guess what what Katie, 
NOTE Confidence: 0.27132082
00:43:45.770 --> 00:43:47.244 12 years or or more,
NOTE Confidence: 0.27132082
00:43:46.850 --> 00:43:47.244 right.
NOTE Confidence: 0.27132082
00:43:47.244 --> 00:43:49.608 And we now have tumor tissue, 
NOTE Confidence: 0.27132082
00:43:49.610 --> 00:43:52.140 germline DNA pretreatment and that
NOTE Confidence: 0.27132082
00:43:52.140 --> 00:43:54.442 resistance and working with Rick
NOTE Confidence: 0.27132082
00:43:54.442 --> 00:43:56.366 Lifton a number of years back before
NOTE Confidence: 0.27132082
00:43:56.366 --> 00:43:57.849 he left and and his lab,
NOTE Confidence: 0.27132082
00:43:57.850 --> 00:44:01.084 we we sequenced all those tumors.
And very interestingly you can see here the 14 tumors and you can see the first response shown here in green and the resistance shown in the yellow triangle.

So we had pre and post samples on patients who responded and then became resistant to immune therapy. And you can see it was from a hodgepodge of different trials, some with anti PDL 1, some with anti PD. One the drugs are different but quite frankly for this type of analysis I don’t think it makes much of a difference.

Well, two stories emerge from this.
They’ve both been published several years back, one that that Katie and Scott LED where we actually had one patient. This patient was on Tremolomab and Debiolomab had a tumor that responded and then it became resistant. And actually by looking at the biopsies pre and post, we didn’t see much different in PDL one. But what we did see is this is loss of beta 2 microglobulin. So if you look at copy number, there was already lost a pre immunotherapy. The patient had already lost one copy of Beta 2 microglobulin.
And then when the patient became resistant, they lost both copies of Beta 2 blackroglobulin and Beta 2 microglobulin of course is an essential component of MHC one. So these tumors lost the ability to present neo anakin to T cells. So we are actually seeing that about five to 10% of the time in lung cancer. We need to use other other ways. Maybe the innate immune system’s going to be the way we target these tumors and K cells or something like that.
And then what Kurt and David did is this is quantitative amino fluorescence. We took a whole bunch of samples of responders, non responders. These are samples that Scott had collected over the years and we looked at those samples and we stained for CD3 and when double labeling and we looked at CD3. So we looked for tumors that were low CD3, so low T cells. We looked at tumors that were low CD3, high CD3 and low grand Simon Ki 67 and the idea there were these are tumors that were not activated in their T cells.
And then we looked at some tumors that were high CD3 and high Granzyme and KS 67 and that Granzyme and KS 67 are the white and the green.

And I would have predicted that this is the group Group C here that would have done the best. But interestingly the group that did best was you can see here's type 2 group shown here, high CD3 and low granzyme and low KS 67.

So why is the group that has many T cells but has the non activated T cells doing better? And that was something we really
00:46:24.208 --> 00:46:25.764 couldn’t explain until recently when
NOTE Confidence: 0.75460684
00:46:25.764 --> 00:46:27.620 Li Ping Chen and and Kurt and others.
NOTE Confidence: 0.75460684
00:46:27.620 --> 00:46:30.511 Miguel Sanam Ahmed who was in Li
NOTE Confidence: 0.75460684
00:46:30.511 --> 00:46:32.700 Ping’s lab did a study and actually
NOTE Confidence: 0.75460684
00:46:32.700 --> 00:46:34.060 using citep analysis showed that
NOTE Confidence: 0.75460684
00:46:34.116 --> 00:46:35.551 many of those T cells that are
NOTE Confidence: 0.75460684
00:46:35.551 --> 00:46:36.939 in the tumor are burned out,
NOTE Confidence: 0.75460684
00:46:36.940 --> 00:46:38.128 they’re they’re not active.
NOTE Confidence: 0.75460684
00:46:38.128 --> 00:46:39.613 And it probably explains why
NOTE Confidence: 0.75460684
00:46:39.613 --> 00:46:40.835 chemotherapy works with immunotherapy
NOTE Confidence: 0.75460684
00:46:40.835 --> 00:46:42.300 because chemotherapy kills the T
NOTE Confidence: 0.75460684
00:46:42.300 --> 00:46:44.115 cells that are in the tumor micro
NOTE Confidence: 0.75460684
00:46:44.115 --> 00:46:45.300 environment making room for more
NOTE Confidence: 0.75460684
00:46:45.300 --> 00:46:47.100 active and newer T cells to come in.
NOTE Confidence: 0.75460684
00:46:47.100 --> 00:46:48.864 This is a work in progress and we need
NOTE Confidence: 0.75460684
00:46:48.864 --> 00:46:50.578 fresh tumor samples to study this more.
But the idea is that it’s the quality of the T cells of the tumor that matters, not just whether the T cells are there or not. In the last few minutes, I just want to tell you about one more story and that’s how we look at resistance. So what we’re thinking here in our group is when we looked at 250 cases of lung cancer, you can see that about 70% of these tumors were high PDL one and high kill. So they have a lot of PDL one and
a lot of T cells in the tumor.

These are probably the tumors that responded quite well to immunotherapy.

But here’s another 26% of tumors that have high tail.

There’s a lot of blue but no PDL 1, so probably suggest there’s another checkpoint in play.

And then very interestingly 45 or twenty-seven percent of lung cancers are cold.

So it’s really these type 1 tumors.

I’ve already talked to you about.

These are the type 2.

I’m sorry, these, these are the tumors that probably respond.

have a durable responder, Maureen.
They either require resistance like I just showed you or they’re probably resistant for mechanisms we don’t yet understand.

But it’s the other other tumor types that we’ve been targeting in the spore and type three of the tumors that must have some other checkpoint.

So Li Ping and you know, I became involved with this ’cause I did a sabbatical in this lab in 2015 and they were working on this project.
he said sure he was developing it with a company called Nexcure and this is a drug known as cyclic 15 and I'm running low on time, but basically this is a homolog to PDL one and in in tumors that are interferon high, you know that activates PDL one, but it actually down regulates cyclic 15. So it makes sense that this, this marker, this protein might be more important in tumors that are PDL one negative and actually that’s been shown. So here’s cyclic 15 and here’s PDL one and you can see in
tumors that have cyclic 15, it's a suppressor of T cells. So the idea was could this be an alternate target we can use in these tumors that are low in PDL one and the answer is yes, we were involved in the phase one trial, Pat Larusso was API on that. We did that with a company, There's a company sponsored trial. Often times you have to do the first trial with a company and then your next trial can be your own Ind. So the first trial was a company sponsored trial and you can see.
Here’s patients two patients with lung cancer who had response, one with a complete response, one with a partial response. That response and lung cancer wasn’t here at Yale but this was a patient who had already had immunotherapy and failed and you can see they’re responding to the CIGLIC 15. But the phase one team we Katie Kirk was here we got a nice picture at least she she did the picture not me she had her own photographer with and then this is what I want to show you. Scott Gettinger has these data I presented on his behalf because 110
He couldn’t make the meeting. But this is Scott’s work. Scott has led a trial of NC 318, which is the antibody against ciglictin 15 and this is totally investigator initiated. Yale holds the I and D we’ve put almost 40 patients on this trial. We have two arms of the drug alone, different schedules. Then we combine the drug with pembrolizumab, the PD1 inhibitor. We also have an arm of IO naive patients. We’re just starting, so we’ve been studying this here at Yale.
We’ve been getting biopsies pre and post and again I don’t have a lot of time left, but I’ll just get cut to the chase.

The biomarker that David’s been developing has been helpful to date.

We as always happens, we don’t get biomarker on the patients that have the best response.

We actually just had another response yesterday.

So stay tuned.

But what we have done is we’ve looked at patients and we’ve looked at a number of patients have benefited some of them that are getting pembrolizumab plus cyclip 15 and
some of them cyclip 15 alone.
And you can see we’re seeing PRS, I’ll tell you as someone who works in this field of lung cancer to see an immuno refractory patient respond, you can count on one hand how often that happens with some of these new agents. So we’re very excited about this. We’re trying to understand the molecular mechanisms, but we’ve had four responders now to the combo and one to a single agent and actually pictures are worth 1000 words. So here’s that patient who had got the single agent liver lesion that’s
responded and here are three examples
NOTE Confidence: 0.66993445
00:50:48.685 --> 00:50:51.096 of patients who are responding to the combo.
NOTE Confidence: 0.66993445
00:50:51.100 --> 00:50:52.788 So we are seeing activity here
NOTE Confidence: 0.66993445
00:50:52.788 --> 00:50:54.362 and we're in the process of working
NOTE Confidence: 0.66993445
00:50:54.362 --> 00:50:55.989 with next Cure and with other other
NOTE Confidence: 0.66993445
00:50:55.989 --> 00:50:58.560 groups to decide what our next trial will be.
NOTE Confidence: 0.66993445
00:50:58.560 --> 00:51:00.020 So I'm going to skip this.
NOTE Confidence: 0.66993445
00:51:00.020 --> 00:51:01.497 I'm running, I was very ambitious.
NOTE Confidence: 0.66993445
00:51:01.500 --> 00:51:04.416 I haven't given our live talk in many years,
NOTE Confidence: 0.66993445
00:51:04.420 --> 00:51:04.657 OK.
NOTE Confidence: 0.66993445
00:51:04.657 --> 00:51:06.553 But what I do want to tell you
NOTE Confidence: 0.66993445
00:51:06.553 --> 00:51:08.216 about is just get to the end.
NOTE Confidence: 0.66993445
00:51:08.220 --> 00:51:11.379 So what I've tried to show you today is
NOTE Confidence: 0.66993445
00:51:11.380 --> 00:51:13.456 we're making progress in this disease.
NOTE Confidence: 0.66993445
00:51:13.460 --> 00:51:14.508 It’s really phenomenal progress.
NOTE Confidence: 0.66993445
00:51:14.508 --> 00:51:16.080 It doesn’t always seem like that
if you’re on the inside, but you know if you look back at it from a 2030 year perspective, we now have patients with lung cancer. Ironically the patients who are smokers who have many more mutations probably have the chance of cure with immunotherapy and as we move that immunotherapy earlier maybe even more so. But the targeted therapy produces amazing benefit and quality of life and if we use it earlier I believe we could probably cure some patients there as well. The theme I think of of Yale as a
whole and certainly of the lung group
is that we used to call these Darts.
but our clinical trials team uses
the institutional science and our
industry collaborations to develop
trials that lead to advances grants
and we're feeding on that cycle
we're building a team that's
focusing on lung cancer advances.
We have many other you know targets.
We're working with Aaron Rings,
Teen BP and the Melanoma group
and the lung group as well.
CD 93 is a target for vascular permeability.
We're starting to work with
here at Yale with Lee

Ping and other other targets.

And I didn’t know Don was going to be here, but you know we’re certainly interested in the flip as well.

We’re doing trials.

This is an example of a biomarker adaptive trial we did with Merck.

But I’d rather tell you about the trial that we’re developing in the last minute called the Bulldog trial and Maina’s here.

So Maina’s been coordinating with us doing a great job.

How are we going to do another
00:52:39.030 --> 00:52:40.595 battle trial here at Yale?
NOTE Confidence: 0.43922126

00:52:40.600 --> 00:52:42.608 What I would suggest is we have to
NOTE Confidence: 0.43922126

00:52:42.608 --> 00:52:44.376 pull together and and do a trial
NOTE Confidence: 0.43922126

00:52:44.376 --> 00:52:46.187 where we now take advantage of the
NOTE Confidence: 0.43922126

00:52:46.187 --> 00:52:47.837 pathology that I’ve shown you today
NOTE Confidence: 0.43922126

00:52:47.840 --> 00:52:49.952 of the science here at Yale and of
NOTE Confidence: 0.43922126

00:52:49.952 --> 00:52:52.090 our ability to do clinical trials and
NOTE Confidence: 0.43922126

00:52:52.090 --> 00:52:54.160 lead that next generation of studies.
NOTE Confidence: 0.43922126

00:52:54.160 --> 00:52:57.152 And we are now looking for new ideas.
NOTE Confidence: 0.43922126

00:52:57.152 --> 00:52:57.704 Here’s,
NOTE Confidence: 0.43922126

00:52:57.704 --> 00:53:00.074 here’s our current idea that we’ve
NOTE Confidence: 0.43922126

00:53:00.074 --> 00:53:01.264 been shopping around and we’ve
NOTE Confidence: 0.43922126

00:53:01.264 --> 00:53:02.608 had meetings with three different
NOTE Confidence: 0.43922126

00:53:02.608 --> 00:53:04.376 pharma groups in the last month
NOTE Confidence: 0.43922126

00:53:04.376 --> 00:53:05.316 and they’re all interested.
NOTE Confidence: 0.43922126

00:53:05.316 --> 00:53:07.159 So we’ll have to see who works with us.
We're really excited about this and we're going to do real time tumor blood,
real time immune profiling. We can do that here. We can do it in a clear appropriate way.
And then we're going to initially equally randomized patients to treatments.
But then once we learn about how these biomarkers pretend response,
we're going to do a biomarker enrichment, adaptive randomization and Steve Miles very excited to do that with us.
Here's the team that's working on that, just the core team,
but we'll be getting everyone
involved very soon.

So as I conclude, can we cure metastatic lung cancer?

Yes, I couldn’t have said that 10 years ago, but only in some cases.

We have 12 plus year survivors from our very first trials.

Treatment was well tolerated and retreatment was possible.

I didn’t show you that, but sometimes you can retreat,

but we don’t even know what the markers are for that.

But the problem is we don’t have any way of knowing this in advance.

We’ve got to do more biomarker work.
00:53:59.240 --> 00:54:01.277 So do we need to personalize immunotherapy?

NOTE Confidence: 0.43922126

00:54:01.280 --> 00:54:01.873 Absolutely.

NOTE Confidence: 0.43922126

00:54:01.873 --> 00:54:04.838 We spent 20 years personalizing targeted therapy.

NOTE Confidence: 0.43922126

00:54:04.840 --> 00:54:05.496 You’ll you’ll hear about that next June 10th, but we’re still not there yet.

NOTE Confidence: 0.43922126

00:54:05.496 --> 00:54:11.846 We need biomarkers and better combos.

NOTE Confidence: 0.43922126

00:54:09.890 --> 00:54:13.610 We need innovative trial designs.

NOTE Confidence: 0.43922126

00:54:13.610 --> 00:54:15.766 But the future for this is now,

NOTE Confidence: 0.43922126

00:54:15.770 --> 00:54:17.030 so last slides,

NOTE Confidence: 0.43922126

00:54:17.030 --> 00:54:19.130 we need to personalize immunotherapy,

NOTE Confidence: 0.43922126

00:54:19.130 --> 00:54:20.510 identify biomarkers and

NOTE Confidence: 0.43922126

00:54:20.510 --> 00:54:21.890 improve combination therapy,

NOTE Confidence: 0.43922126

00:54:21.890 --> 00:54:23.542 identify new targets and

NOTE Confidence: 0.43922126

00:54:23.542 --> 00:54:24.368 rational combinations,
establish novel endpoints,
NOTE Confidence: 0.43922126
00:54:25.870 -- 00:54:27.370 innovative trial designs.
NOTE Confidence: 0.43922126
00:54:27.370 -- 00:54:28.530 We can do that here,
NOTE Confidence: 0.43922126
00:54:28.530 -- 00:54:30.190 address mechanisms of resistance
NOTE Confidence: 0.43922126
00:54:30.190 -- 00:54:31.850 and bring disease early.
NOTE Confidence: 0.43922126
00:54:31.850 -- 00:54:34.685 It’s sort of reads like the CCSG.
NOTE Confidence: 0.43922126
00:54:34.690 -- 00:54:35.458 We can do it,
NOTE Confidence: 0.43922126
00:54:35.458 -- 00:54:36.926 but I’m just my charge on this
NOTE Confidence: 0.43922126
00:54:36.926 -- 00:54:38.528 first ground round to the Friday.
NOTE Confidence: 0.43922126
00:54:38.530 -- 00:54:41.050 To the fellows, the scientists here,
NOTE Confidence: 0.43922126
00:54:41.050 -- 00:54:42.034 the translational scientists,
NOTE Confidence: 0.43922126
00:54:42.034 -- 00:54:42.362 everyone.
NOTE Confidence: 0.43922126
00:54:42.362 -- 00:54:44.002 We’re we’re a continuum from
NOTE Confidence: 0.43922126
00:54:44.002 -- 00:54:45.652 the clinic and the lab working
NOTE Confidence: 0.43922126
00:54:45.652 -- 00:54:46.927 together to help the patient.
NOTE Confidence: 0.43922126
00:54:46.930 -- 00:54:48.850 We need to develop drugs in real time,
and it’s only going to be with science. Ben Lewis here, He gave an amazing talk the other day on a trial that we’re doing with ipilumab, nivolumab biomarkers. That’s going to be the future. But then to translate those into new studies, So I’ll just end with a picture. So this is Ben’s talk. The other day we had 50 people at a translational lung meeting. Katie and Sarah have been organizing this. This is how we’re going to make progress. We have to meet on a regular basis, go over our science,
do as many IIs as we can.

This trial actually was a trial of ipilumab,
nivolumab that we went to meet

Several of us, and we're not running it under our own ID,

but we're getting the samples.

We just got to get the samples

here and get the science here.

So we can make the next step.

So with that I'll just end

by saying save the date.

Katie and I and the whole
committee are gonna hold the

interest for meeting here next
June and we’re gonna be celebrating 20 years of EGFR mutations. The guest list is everyone’s saying yes and we’re gonna we’re the hotels will be full. So with that off, thank you very much. It’s it’s the hour. But I’m happy to take one or two questions I’m supposed to look online a lot of people online. Oh, here’s a question. Can you comment on giving the therapy of the new immunotherapy and the accurate
setting does seem to have some benefit.

The results are a bit mixed with the tezalizumab in a trial known as Keno 10 in the accurate setting in patients that were PDL one more than 1%, the hazard ratio is about point 6.7. So there is, there is a benefit but when you look at those patients who were PDL one negative in their initial sample, there was no benefit at all. Hembalizumab interestingly in a very similar trial didn’t see any biomarker prevalence but they did see a benefit as well. My sense is that neoadjuvant is probably better because when you and
and it comes from Melanoma I see
Marcus shaking his head yes in in
Melanoma and in lung cancer you you
have a tumor and you have the lymph
nodes that are involved as well.
So if you use your your immunotherapy
in the Neoactivate setting you’ve got
the tumor in situ in its micro
environment with its lymph nodes.
So you really get the entire T cell
micro environment I think you know affected.
So it’s it’s better.
The problem is we’re only going
to be able to do neo activate on
a selected group of patients.
What we’re seeing now is I’m sorry I didn’t have time to show those data, but you know it works but you have

to pick carefully because you’re not going to really take someone who’s not a candidate for surgery

So we have to be somewhat selective.

But at tumor board we’ll look at a case, we’ll say this patient looks like they’re surgically resectable they can take the three months to get the neoadjuvant therapy and and we’re treating those patients in that way.

Some of them might not be in that situation

And and chemo radiation David you know is,
is very is with immunotherapy
is also very beneficial.
So we have multiple options.
I’ll leave you with this word.
Everyone should get immunotherapy in some way if they can.
They, the patients that don’t get immunotherapy would be ones who have autoimmunity or some reason that they’re intolerant or certainly those with molecular drivers because in those cases we know immunotherapy doesn’t seem to work as well.
But I’d say if there’s any hint of metastatic disease,
00:58:01.660 --> 00:58:03.716 I try to find ways that I can
NOTE Confidence: 0.26020557
00:58:03.716 --> 00:58:04.980 give immunotherapy to a patient.
NOTE Confidence: 0.26020557
00:58:04.980 --> 00:58:05.180 Yes,
NOTE Confidence: 0.26020557
00:58:05.180 --> 00:58:05.380 because
NOTE Confidence: 0.28358683
00:58:07.860 --> 00:58:07.940 you
NOTE Confidence: 0.28358683
00:58:10.220 --> 00:58:12.597 give her her expression so much more comment.
NOTE Confidence: 0.28358683
00:58:12.597 --> 00:58:16.770 Any thoughts on have we target that or why
NOTE Confidence: 0.28358683
00:58:16.770 --> 00:58:18.914 doesn’t EGFR inhibition work for those?
NOTE Confidence: 0.28358683
00:58:18.914 --> 00:58:19.766 Yeah, we we’ve tried that.
NOTE Confidence: 0.28358683
00:58:19.766 --> 00:58:21.330 In fact that was the mark as we worked
NOTE Confidence: 0.28358683
00:58:21.330 --> 00:58:22.749 at an MD Anderson and actually we worked
NOTE Confidence: 0.28358683
00:58:22.749 --> 00:58:24.285 with Jose Bazaga on that many years ago.
NOTE Confidence: 0.28358683
00:58:24.285 --> 00:58:26.174 We thought it would be EGFR
NOTE Confidence: 0.28358683
00:58:26.174 --> 00:58:27.610 expression and and that is helpful.
NOTE Confidence: 0.28358683
00:58:27.610 --> 00:58:28.786 You know, if you’re using an
NOTE Confidence: 0.28358683
00:58:28.786 --> 00:58:30.106 antibody that could be, you know,
if you’re using satuximab in, in certain tumors. But but it really isn’t, it’s not, it’s not the absolute level of EGFR but it’s the quality, it’s whether it’s being driven by those mutations and you know the TKI is you know where the you know if you’ve got that addicted tumor that then the TKI is will have that amazing effect. But you know the expression can be helpful maybe for AD CS right now, now now there’s a whole new now that now that we’re sort of at a standstill with a new immunotherapy.
resistant drugs and with new targeted drugs for EGFR resistance.

We’re using the address now with with payloads. So that might be an area done since early detection, this subject key piece puzzle, what are your thoughts on possible innovation?

Well certainly you know there’s the easy one which is screening which now with helical CTS and low dose CTS it does pick lung cancers up earlier and it’s been shown to improve survival. You know in the US only about 7% of patients eligible for screening get screened. You know the criteria were a bit
Strictly speaking, they've been reused a bit, but you know it has to have been someone who’s had a smoking history.

So of course it doesn’t take into account any of these patients who are the never smokers or the light smokers which are the ones that have these different mutations.

Certainly you know looking in the DNA and CTDNA think that’s going to be the way to go.

We’re already using that for minimal residual disease both to determine whether or not patients need more therapy and now of course we can look at...
the quality of what we’re finding, you know what are the new mutations, those techniques are getting more and more sensitive. I’ll tell you in the enduro trial we only picked up you know post resection a sample 1020% of the time. So. So even though many of them, many more of them probably did have residual disease, but it’s getting more and more sensitive. Now you asked about you know, screening someone with a history or family history or will we think we need a lot more work to do that.
But you know the techniques are getting so much more sensitive. Certainly if you know that someone has a tumor or if they have Melanoma, you know what the antigens are. So you know what panel to look for and lung cancer which has so many different types of mutations there is what Charlie Swanton is doing now and I would put my money on his approach. You know there would be spoke models where you actually can sequence a tumor and get a panel of mutations and that makes your sensitivity much more.
much better

and you know that’s something

we’ve talked about and maybe I know

david and I have talked about it in

both david’s you know we don’t we don’t

you need AI, you need pre

competitive collaboration,

you need big data sets.

There’s a meeting in two weeks at

the National Academy of Medicine

on public private partnerships

and you know data sharing.

We’re going to have the editors of
some of the big journals there.

We’re going to have people from UK Welcome Trust from the NCI.

That’s, that’s what we need to take these big approaches,

large sample sets that’s love to talk to you more about that get your ideas.

I think we better stop because it’s late.

I’m starting to go a little over.

But thank you all for coming.

It’s it’s exhilarating to see people in the talk to a live audience.

So. So thank you.