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 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
that 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 you know, and it’s amazing at Yale 44 years ago and my Pecam professor’s in the front row, Don Engleman and it’s amazing to see you and you know, and I actually wasn’t his course like he would probably be but it’s you know, Yale’s just a phenomenal place.
00:01:55.342 --> 00:01:57.442 me to be to be here and I gave
NOTE Confidence: 0.46130416
00:01:57.442 --> 00:01:58.959 a grand rounds about 12 years
NOTE Confidence: 0.46130416
00:01:58.959 --> 00:02:00.399 ago when I first arrived.
NOTE Confidence: 0.46130416
00:02:00.400 --> 00:02:02.200 So a little bit of progress
NOTE Confidence: 0.46130416
00:02:02.200 --> 00:02:04.016 since then and I'll show you
NOTE Confidence: 0.46130416
00:02:04.016 --> 00:02:05.680 that now my disclosures.
NOTE Confidence: 0.46130416
00:02:07.760 --> 00:02:11.915 So we're back. This was last week at
NOTE Confidence: 0.46130416
00:02:14.080 --> 00:02:16.352 East Haven. We had our ASCO review and
NOTE Confidence: 0.46130416
00:02:16.352 --> 00:02:18.997 and a dinner for some of the faculty.
NOTE Confidence: 0.46130416
00:02:19.000 --> 00:02:20.944 It was just great to see so many
NOTE Confidence: 0.46130416
00:02:20.944 --> 00:02:22.558 people there and the spirits there.
NOTE Confidence: 0.46130416
00:02:22.558 --> 00:02:24.250 We had a great day discussing
NOTE Confidence: 0.46130416
00:02:24.305 --> 00:02:26.078 all of our different divisions,
NOTE Confidence: 0.46130416
00:02:26.078 --> 00:02:29.685 both solid and liquid advances in the
NOTE Confidence: 0.46130416
00:02:29.685 --> 00:02:32.043 field and it's good to see so many
NOTE Confidence: 0.46130416
00:02:32.043 --> 00:02:34.143 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, we had radiation oncology. 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 new cases in the US with over 130,000 deaths. So this is the reason there’s so much research and pharmaceutical
NOTE Confidence: 0.46130416
00:03:29.932 --> 00:03:31.480 development in this area.
NOTE Confidence: 0.46130416
00:03:31.480 --> 00:03:32.968 84% of lung cancer is non
NOTE Confidence: 0.46130416
00:03:32.968 --> 00:03:33.960 small cell lung cancer.
NOTE Confidence: 0.46130416
00:03:33.960 --> 00:03:35.936 A a great effort now still with small
NOTE Confidence: 0.46130416
00:03:35.936 --> 00:03:37.964 cell lung cancer used to be that
NOTE Confidence: 0.46130416
00:03:37.964 --> 00:03:39.439 was only associated with smokers.
NOTE Confidence: 0.46130416
00:03:39.440 --> 00:03:40.840 It’s still mostly with smokers.
NOTE Confidence: 0.46130416
00:03:40.840 --> 00:03:42.560 But now we know that EGFR mutated lung
NOTE Confidence: 0.46130416
00:03:42.560 --> 00:03:43.988 cancer can develop into small cell
NOTE Confidence: 0.46130416
00:03:43.988 --> 00:03:45.658 lung cancer and Sheng lives in the
NOTE Confidence: 0.46130416
00:03:45.658 --> 00:03:47.242 2nd row sort of leads to that effort
NOTE Confidence: 0.46130416
00:03:47.242 --> 00:03:49.960 here and she’ll probably give a grand round.
NOTE Confidence: 0.46130416
00:03:49.960 --> 00:03:50.560 Oh yeah,
NOTE Confidence: 0.46130416
00:03:50.560 --> 00:03:50.860 please.
NOTE Confidence: 0.46130416
00:03:50.860 --> 00:03:52.360 It is a little distracting
NOTE Confidence: 0.61711353
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, you know, you know, 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, Paclitaxel, 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 because New Haven is a community where smoking is higher 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 actually know driver mutations so we can target those. This is why so many people want to work in this field because 20 years ago each GFR mutations were identified. So we actually know driver mutations so we can target those. But there are now at least ten other targetable alterations and we're...
00:06:30.260 --> 00:06:32.672 seeing evidence of 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, 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 of a lag 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 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,
four years old.
So I think this,
this shows some of the targeted therapies
this I’ll talk about in the first
half of the talk and the immunotherapy
benefits are are still on the horizon.
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 you know it's a team approach to lung cancer and you can see there's Dan Lynn Tenui from pulmonary, Sarah Goldberg who unfortunately can't be here today, and Frank Getterbach, Sarah Goldberg 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 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. And we also have a spore. 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 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 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

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,
you know young investigators

who aren’t working lung cancer,

we’re getting them involved in lung cancer

we could have 10 projects on the SPORE.

The problem is you can really only have three projects on these grants because the NCI continues to cut the funds.

We have developmental funds and and donor funds we used to enhance it.

But look at this,

all the different departments that are involved,

it’s building a community of lung cancer here at Yale.

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.
00:11:27.524 --> 00:11:29.178 in the community of lung Cancer Research.
NOTE Confidence: 0.35788172
00:11:29.180 --> 00:11:30.762 And then I just want to give
NOTE Confidence: 0.35788172
00:11:30.762 --> 00:11:32.180 a little shout out to Katie.
NOTE Confidence: 0.35788172
00:11:32.180 --> 00:11:33.935 So we had a little we went to New
NOTE Confidence: 0.35788172
00:11:33.935 --> 00:11:35.627 York last week and maybe two weeks
NOTE Confidence: 0.35788172
00:11:35.627 --> 00:11:37.535 ago now and Katie was honored by
NOTE Confidence: 0.35788172
00:11:37.535 --> 00:11:39.020 the Lung Cancer Research F oundation
NOTE Confidence: 0.35788172
00:11:39.020 --> 00:11:41.350 and see the multi modality in this
NOTE Confidence: 0.35788172
00:11:41.350 --> 00:11:43.575 Shen Liu of the Sheriff Pathology
NOTE Confidence: 0.35788172
00:11:43.575 --> 00:11:44.700 Valentina from genetics.
NOTE Confidence: 0.35788172
00:11:44.700 --> 00:11:47.458 Some of us really, we’re a community
NOTE Confidence: 0.35788172
00:11:47.458 --> 00:11:49.270 that’s tackling this disease.
NOTE Confidence: 0.35788172
00:11:49.270 --> 00:11:50.306 So now let’s do a little science.
NOTE Confidence: 0.35788172
00:11:50.310 --> 00:11:51.468 I’ve already used 10 minutes up,
NOTE Confidence: 0.35788172
00:11:51.470 --> 00:11:53.507 but you know, I’m always taking pictures.
NOTE Confidence: 0.35788172
00:11:53.510 --> 00:11:55.748 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. 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.
when I was meeting with her,
its all about the mentors
you have and I had worked,
I had been at Yale,
I had worked in Kim Darnell’s
lab at at Rockefeller.
I was very interested in signal
and I was very
transduction and I was very
interested in EGFR and EGFR receptor.
And just around that time the first
small molecules and antibodies
had been developed against EGFR
and we knew that in epithelial
tumors such as lung cancer,
EGFR was up regulated.
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 eg field and these new molecules were coming through and they they offered me the project and I just said sure. And 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 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.
And I was a little scared of her at the time.
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. But back then it took a while. 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
an extended access trial.

People could get it off label while that we were waiting for the drugs to be approved and many patients were treated and of course it was found that in the EGFR receptor, which of course would be a dimer.

This is a simplification in the tyrosine kinase domain. There were specific mutations mostly at that time discovered in exxons 19 and 21. Now we see them in Exxon 20 as well.

And these mutations of course activated and caused this to be a driver.

And then these small molecules bound
00:15:26.574 --> 00:15:28.797 into the ATP binding site and we’re very,
NOTE Confidence: 0.27635187
00:15:28.800 --> 00:15:29.346 very potent.
NOTE Confidence: 0.27635187
00:15:29.346 --> 00:15:30.438 They had some rash,
NOTE Confidence: 0.27635187
00:15:30.440 --> 00:15:31.292 they had some diarrhea,
NOTE Confidence: 0.27635187
00:15:31.292 --> 00:15:32.357 but they were very potent.
NOTE Confidence: 0.5602203
00:15:32.360 --> 00:15:33.920 And that led to this is actually being
NOTE Confidence: 0.5602203
00:15:33.920 --> 00:15:35.799 in a place like MD Anderson patients just
NOTE Confidence: 0.5602203
00:15:35.799 --> 00:15:38.037 flowed in and we had a big phase one clinic.
NOTE Confidence: 0.5602203
00:15:38.040 --> 00:15:40.101 I think we must have treated a couple 100
NOTE Confidence: 0.5602203
00:15:40.101 --> 00:15:41.887 patients in the first two or three years and
NOTE Confidence: 0.5602203
00:15:41.887 --> 00:15:43.920 I LED the trial and that’s Cicely Harris.
NOTE Confidence: 0.5602203
00:15:43.920 --> 00:15:45.635 She was one of the first patients.
NOTE Confidence: 0.5602203
00:15:45.640 --> 00:15:46.949 And, you know, she was written up
NOTE Confidence: 0.5602203
00:15:46.949 --> 00:15:48.315 in the Wall Street Journal because
NOTE Confidence: 0.5602203
00:15:48.315 --> 00:15:49.839 the idea was we probably didn’t.
NOTE Confidence: 0.5602203
00:15:49.840 --> 00:15:50.836 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 of the cancer and this just shows that 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, they went with the Pharmacia product and made a bit of a mistake because this drug 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 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. This is just an example and again I'm just giving you a bit of an overview today. The most common mutation for resistance is known as T790M and the patients that have that this drug wasimertinib was first studied to target that resistance mutation which is about 50% of the resistance which was seen there over 60-70% 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 we put about 100 and 120 patients on lung trials in a Goodyear there we’re putting three or 400 patients on trial. But what I noticed I was leading the group lung group there is we’re doing it on 20 different trials.
So we said we can do one trial and use biomarkers to decide who should get which drug. This wasn’t easy because if you have a group of 20 people, everyone has their own favorite 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 used a little bit of push and pull because the science was exciting and at that time...
and David Meta who’s here now, I work with him at that time we could get biopsies.

Core biopsies, prior to 2004, 2005, most lung cancer biopsies were fine needle aspirations. You had a little bit of few cells, you didn’t have really enough tissue for sequencing.

But now that sequencing was coming to to bear. We said can we do a trial called Battle and we worked with a pathologist, Ignacio Astuba Jack Lee,
a biostatistician,

NOTE Confidence: 0.27161515

Ed Kim now at City of Hope and

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with our mentor Wang Ki Han.

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We developed a trial we called Battle

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and what we called it is biomarker

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integrated approach of targeted

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therapy for lung cancer elimination.

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So what we did is we had four

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or five different drugs.

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We did a biopsy.

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We got the result within 14 days

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and then we used that result to say

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this patient has an EGFR mutation,

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they should go on heratinib.

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This patient has a VEGF up regulation,

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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 at MD Anderson but we started doing a tissue based approach and the team started to work together and that’s how we were doing that. Actually funded by an RO one that I brought with me from Anderson. But moving to the what I want to tell you about 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 10-15% 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 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, 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.
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,
00:23:43.970 --> 00:23:47.534 so we actually got a call it was in April.
00:23:47.534 --> 00:23:49.850 We we looked at the data and and
00:23:49.850 --> 00:23:51.845 actually the hazard ratio I’ll show you
00:23:51.845 --> 00:23:54.145 in a moment was so good that you’ll
00:23:54.145 --> 00:23:56.359 you’ll see where things went after that.
00:23:56.360 --> 00:23:57.356 So this is what we saw.
00:23:57.360 --> 00:24:01.196 it was Good Friday and Passover,
00:24:01.200 --> 00:24:02.680 I I’ll go with Passover,
00:24:02.680 --> 00:24:03.720 but you can see here,
00:24:03.720 --> 00:24:05.475 here it was in in that year the
00:24:05.475 --> 00:24:07.101 stakes 1B and 3A patients here are
00:24:07.101 --> 00:24:08.574 patients who got the acid mertinib
00:24:08.574 --> 00:24:10.092 in the adjuvant setting and here
00:24:10.092 --> 00:24:12.220 is the control and the hazard ratio
53
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.

This is the, this is actually the review at the time when it would have normally 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 from recurring. Now where do you think
00:24:41.560 --> 00:24:43.580 the disease is kept from recurring from?
00:24:43.580 --> 00:24:46.012 Well, the first, I guess we'll show you
00:24:46.012 --> 00:24:49.800 that all all parameters benefited sex,
00:24:49.800 --> 00:24:51.452 age, whether or not the patient was
00:24:51.452 --> 00:24:53.896 a prior smoker, Asian or non Asian,
00:24:53.896 --> 00:24:55.660 all three stages, both mutations.
00:24:55.660 --> 00:24:57.960 So you always do better with XN 19 deletion,
00:24:57.960 --> 00:25:01.299 it’s a loss of it’s a deletion versus the
00:25:01.299 --> 00:25:04.638 point mutation which can revert a bit
00:25:04.640 --> 00:25:05.954 When you look at a forest pot like that,
00:25:05.960 --> 00:25:07.318 for those who aren’t used to it,
00:25:07.320 --> 00:25:10.440 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 of on the treatment job 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.
00:25:38.150 --> 00:25:39.082 brain, liver and bone.

00:25:39.082 --> 00:25:40.480 And actually we looked at that

00:25:40.529 --> 00:25:41.849 and this is pretty phenomenal.

00:25:41.850 --> 00:25:43.264 This is looking at the brain as

00:25:43.264 --> 00:25:44.529 the first site of recurrence,

00:25:44.530 --> 00:25:45.570 which is a major issue.

00:25:45.570 --> 00:25:47.604 If you ask a patient with lung cancer,

00:25:47.610 --> 00:25:48.842 he or she will tell you I’m

00:25:48.842 --> 00:25:49.650 worried about my brain.

00:25:49.650 --> 00:25:52.404 We just had AEAB for our spore last Monday.

00:25:52.410 --> 00:25:53.450 That’s exactly what our

00:25:53.450 --> 00:25:54.490 patient advocate told us.

00:25:54.490 --> 00:25:57.140 But you can see here’s patients adjuvant

00:25:57.140 --> 00:25:58.790 disease who got last Emergenib.

00:25:58.790 --> 00:26:00.350 Here’s the control group hazard
ratio for recurrence in the brain
NOTE Confidence: 0.5093791

meaning a 76% decrease in the first recurrence being in the brain.
NOTE Confidence: 0.5093791

So it’s keeping the tumor from the brain.
NOTE Confidence: 0.5093791

We’ll do this forever probably not but it did it for a long period of time.
NOTE Confidence: 0.5093791

We treated for three years and here you can see now everyone
NOTE Confidence: 0.5093791

was sceptical you know I don’t I
NOTE Confidence: 0.5093791

I never used to do the Twitter.
NOTE Confidence: 0.5093791

Then I started doing the Twitter
NOTE Confidence: 0.5093791

because people said you have to
NOTE Confidence: 0.5093791

read the Twitter because people are being critical of your data.
NOTE Confidence: 0.5093791

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 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 pretty 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 the 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. OK. Now you see the overall survival both if patients get 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 we we we we we

we suggest that patients get

And then

you know the the big critique

of this trial and for those that

read the New England Journal,

there’s there’s a letter I 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 ostomertinib. But the drug wasn’t even improved in the front line setting when we started the trial. So well it’s not perfect, it’s not a perfect would would 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

rack and it does cause some diarrhea

there’s always going to be added

toxicity 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 we’re doing a bunch of

00:30:03.595 --> 00:30:04.189 translational analysis.

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,

NOTE Confidence: 0.29164207
which he studies and Katie studies these as well.

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 osteomerostradium. 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,
00:30:39.670 --> 00:30:41.110 so more than 3 centimeters.
00:30:41.110 --> 00:30:42.014 Everyone always calls me
00:30:42.014 --> 00:30:43.144 what about the small tumors,
00:30:43.150 --> 00:30:44.788 I think it'll probably work there too.
00:30:44.790 --> 00:30:45.982 But we need to do the trial and
00:30:45.982 --> 00:30:46.967 we’re actually doing a trial where
00:30:46.967 --> 00:30:49.161 when you stop the drug that the the
00:30:49.161 --> 00:30:50.990 brain metastasis started to increase.
00:30:50.990 --> 00:30:52.310 So there might be some patients
00:30:52.310 --> 00:30:53.690 who are cured in my opinion,
00:30:53.690 --> 00:30:55.190 but some who are just having cytostatic
00:30:55.190 --> 00:30:57.381 stability of disease and that’s
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 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 and 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 what should the right end point be, you know in in patients. But I think we’ve shown that disease free survival works. OK. And here’s a little plug for Katie. And don’t have time to talk about this, 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 started this together about 5-7 years ago. Here we are in Cambridge 2017 and 2022 we all look the same and you can see that this is just an amazing collaboration because that’s how we’re really making difference and I got to move on but we’re getting funds and 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.
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 O 6 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
00:34:52.244 --> 00:34:53.190 of the survivor events.

00:34:53.190 --> 00:34:55.134 This is the promise of a phase one trial of new drug development.

00:34:55.134 --> 00:34:56.869 The problem is this is only 15%

00:34:56.870 --> 00:35:00.646 but for This is why everyone wants to work in this field.

00:35:00.646 --> 00:35:01.830 We see a light at the end of the tunnel.

00:35:01.830 --> 00:35:03.310 It’s just a very long tunnel,

00:35:03.310 --> 00:35:04.750 but we know that 15% of patients are going to benefit.

00:35:04.750 --> 00:35:12.560 this trial O:3:00 and basically

00:35:11.060 --> 00:35:12.560 this is an actuarial survival curve because it’s now with more than five years of follow up.
He published this in JCO in 2018 at five years in the refractory setting on 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, 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. These patients have primary resistance.

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, the very 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, 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. And 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 and I’m a little worried about that. But he works on the head and export too. The very the pathologists are your pathologists, your statisticians.
critical core members. For any of these grants, you've got to have a good course and that we always get exceptional thanks to David and Kurt and now Sonia’s working with them. So you can see, I said, David, why is this PDL one marker so, so bad And Li Ping was with us and Li Ping said of course it’s not bad. I discovered it. It’s actually very good, but you just don’t measure it properly. And then David made this slide for me that everyone’s now used and and I make sure the credit was there David.
So everyone uses this and and David has done very well at meetings and and and being involved in the panels. 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, the blue, the Dappy is the nuclei and that and the red is PDL one. 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. Katie deserved 2 awards last week because she and Scott set up this amazing repeat biopsy program. 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 and we
get fresh tissue and we get paraffin,

we make transgenic, we make,

And zenta or pathologist is usually

there 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

ago 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 pembro as a tezalizumab.

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

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 had remembered IRA from cell biology that was when I was at Rockefeller done but still I knew Ira and Ira helped us to get this trial and and with IRA’s group did this work for us the
NOTE Confidence: 0.6175327
00:41:00.911 --> 00:41:02.827 RNA shift and you can see pre and
NOTE Confidence: 0.6175327
00:41:02.827 --> 00:41:04.668 post green is pre yellow is post.
NOTE Confidence: 0.6175327
00:41:04.670 --> 00:41:06.133 You can see this is an example
NOTE Confidence: 0.6175327
00:41:06.133 --> 00:41:07.293 of what’s happening when the
NOTE Confidence: 0.6175327
00:41:07.293 --> 00:41:08.269 immune response is active.
NOTE Confidence: 0.6175327
00:41:08.270 --> 00:41:10.391 So we we understand what the active
NOTE Confidence: 0.6175327
00:41:10.391 --> 00:41:12.317 immune response is how is how do we
NOTE Confidence: 0.6175327
00:41:12.317 --> 00:41:14.230 get this to go on in every patient
NOTE Confidence: 0.6175327
00:41:14.230 --> 00:41:15.658 20% of patients responded in that
NOTE Confidence: 0.6175327
00:41:15.658 --> 00:41:17.396 trial but the other 80% did not
NOTE Confidence: 0.6175327
00:41:17.396 --> 00:41:19.517 and those patients that did not we
NOTE Confidence: 0.6175327
00:41:19.517 --> 00:41:21.202 described in this paper the immune
NOTE Confidence: 0.6175327
00:41:21.202 --> 00:41:23.188 desert you know CD 8 before and
NOTE Confidence: 0.6175327
00:41:23.188 --> 00:41:25.024 after the tumor just laughs at,
NOTE Confidence: 0.6175327
00:41:25.030 --> 00:41:26.738 at the PDL 1 inhibitor nothing happens
NOTE Confidence: 0.6175327

93
or you can have a non functional immune response where you have some CD8 cells and maybe a few more posts. But if you look at that immune shift completely flat and then this is actually something we’re seeing more and more of and I don’t have time to talk about it today but our next trial on the sport is going to target this that that the cells that get inhibited that can’t get to the tumor because you get this line of interference and we call this the immune excluded cells. So more to come on this, 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. But the reason I skipped is I’m much more interested to tell you about the future. So we’re now have to target immunotherapy but I showed you at the beginning of my talk was how we used targeted therapy. We understood the target brought it earlier to have the greatest advantage and
I told you about the biobank we have. Well let me show you how it has paid off. So here we had patients who had immune therapy and they responded and then they had more immune therapy. Thanks to that poor protocol that we've had running for I guess what Katie, 12 years or more. And we now have tumor tissue, germline DNA pretreatment and that resistance and working with Rick Lifton a number of years back before he left and his lab.
And very interestingly you can see here the 14 tumors and you can see the first response shown here in the 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.
00:44:26.770 --> 00:44:28.186 They’ve both been published
NOTE Confidence: 0.75460684
00:44:28.186 --> 00:44:29.248 several years back,
NOTE Confidence: 0.75460684
00:44:29.250 --> 00:44:30.930 one that that Katie and Scott LED
NOTE Confidence: 0.75460684
00:44:30.930 --> 00:44:32.450 where we actually had one patient.
NOTE Confidence: 0.75460684
00:44:32.450 --> 00:44:34.448 This patient was on Tremolomab and
NOTE Confidence: 0.75460684
00:44:34.448 --> 00:44:36.573 Debiolomab had a tumor that responded
NOTE Confidence: 0.75460684
00:44:36.573 --> 00:44:38.408 and then it became resistant.
NOTE Confidence: 0.75460684
00:44:38.410 --> 00:44:39.625 And actually by looking at
NOTE Confidence: 0.75460684
00:44:39.625 --> 00:44:41.130 the the biopsies pre and post,
NOTE Confidence: 0.75460684
00:44:41.130 --> 00:44:44.213 we didn’t see much different in PDL one.
NOTE Confidence: 0.75460684
00:44:44.213 --> 00:44:47.330 But what we did see is this is
NOTE Confidence: 0.75460684
00:44:47.330 --> 00:44:49.410 loss of beta 2 microglobulin.
NOTE Confidence: 0.75460684
00:44:49.410 --> 00:44:51.209 So if you look at copy number,
NOTE Confidence: 0.75460684
00:44:51.210 --> 00:44:53.688 there was already lost a pre immunotherapy.
NOTE Confidence: 0.75460684
00:44:53.690 --> 00:44:55.196 The patient had already lost one
NOTE Confidence: 0.75460684
00:44:55.196 --> 00:44:57.010 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. So these patients are going to need more of this. This immune approach won’t work. 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 here's the 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, how, 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 70% 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. I said can we bring this project into the spore? And he,
00:48:09.470 --> 00:48:11.220 he said sure he was developing it
NOTE Confidence: 0.6714045
00:48:11.278 --> 00:48:13.093 with a company called Nexcure and
NOTE Confidence: 0.6714045
00:48:13.093 --> 00:48:14.514 this is a drug known as cyclic
NOTE Confidence: 0.6714045
00:48:14.514 --> 00:48:16.167 15 and I'm running low on time,
NOTE Confidence: 0.6714045
00:48:16.170 --> 00:48:18.807 but basically this is a homolog to PDL one
NOTE Confidence: 0.6714045
00:48:18.810 --> 00:48:21.730 and in in tumors that are interferon high,
NOTE Confidence: 0.6714045
00:48:21.730 --> 00:48:23.248 you know that activates PDL one,
NOTE Confidence: 0.6714045
00:48:23.250 --> 00:48:25.364 but it actually down regulates cyclic 15.
NOTE Confidence: 0.6714045
00:48:25.370 --> 00:48:27.128 So it makes sense that this,
NOTE Confidence: 0.6714045
00:48:27.130 --> 00:48:27.848 this marker,
NOTE Confidence: 0.6714045
00:48:27.848 --> 00:48:28.207 this,
NOTE Confidence: 0.6714045
00:48:28.207 --> 00:48:30.361 this protein might be more important
NOTE Confidence: 0.6714045
00:48:30.361 --> 00:48:32.767 in tumors that are PDL one negative
NOTE Confidence: 0.6714045
00:48:32.770 --> 00:48:34.410 and actually that’s been shown.
NOTE Confidence: 0.6714045
00:48:34.410 --> 00:48:36.072 So here’s cyclic 15 and here’s
NOTE Confidence: 0.6714045
00:48:36.072 --> 00:48:38.039 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.
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 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
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 ciglic 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.
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 of patients who are responding to the combo. So we are seeing activity here and we're in the process of working with next Cure and with other other groups to decide what our next trial will be. So I'm going to skip this. I'm running, I was very ambitious. I haven't given our live talk in many years, OK. But what I do want to tell you is just get to the end. So what I've tried to show you today is we're making progress in this disease. It's really phenomenal progress. It doesn't always seem like that.
00:51:16.129 --> 00:51:17.099 if you’re on the inside,

00:51:17.100 --> 00:51:18.748 but you know if you look back at

00:51:18.748 --> 00:51:20.459 it from a 2030 year perspective,

00:51:20.460 --> 00:51:22.413 we we we now have patients with lung cancer.

00:51:22.420 --> 00:51:24.030 Ironically the patients who are

00:51:24.030 --> 00:51:26.062 smokers who have many more mutations

00:51:26.062 --> 00:51:28.589 probably have the chance of cure with

00:51:28.589 --> 00:51:30.635 immunotherapy and as we move that

00:51:30.635 --> 00:51:32.531 immunotherapy earlier maybe even more so.

00:51:32.540 --> 00:51:34.270 But the targeted therapy produces

00:51:34.270 --> 00:51:36.000 amazing benefit and quality of

00:51:36.057 --> 00:51:37.873 life and if we use it earlier I

00:51:37.873 --> 00:51:39.679 believe we could probably cure some

00:51:39.679 --> 00:51:40.975 patients there as well.

00:51:40.980 --> 00:51:42.906 The theme I think of of Yale as a

NOTE Confidence: 0.66993445
whole and certainly of the lung group

is that we used to call these Darts.

I haven’t made the change the slide,

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

and 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 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?

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

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

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

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

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

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

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

00:52:54.160 --> 00:52:57.159 So we’ll have to see who works with us.

00:52:57.159 --> 00:53:00.074 Here’s, here’s our current idea that we’ve

00:53:00.074 --> 00:53:04.376 been shopping around and we’ve

00:53:04.376 --> 00:53:07.159 had meetings with three different

00:53:07.159 --> 00:53:09.397 pharma groups in the last month

00:53:09.397 --> 00:53:11.069 and they’re all interested.

00:53:11.069 --> 00:53:14.397 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.
So do we need to personalize immunotherapy?
Absolutely. We spent 20 years personalizing targeted therapy.
You’ll hear about that next June 10th, but we’re still not there yet.
We need biomarkers and better combos.
We need innovative trial designs.
But the future for this is now, so last slides,
we need to personalize immunotherapy,
identify biomarkers and improve combination therapy,
identify new targets and rational combinations,
establish novel endpoints,

innovative trial designs.

We can do that here,

address mechanisms of resistance

and bring disease early.

It's sort of reads like the CCSG.

We can do it,

but I'm just my charge on this

first ground round to the Friday.

To the fellows, the scientists here,

the translational scientists,

everyone.

We're we're a continuum from

the clinic and the lab working

together to help the patient.

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, we have to meet on a regular basis, go over our science. So I’ll just end with a picture.

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 Iits 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 and 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 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 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, yeah, so, so new immunotherapy and the accurate
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.

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 and bring them towards 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 and we're treating those patients in that way. Some of them might not be in that situation and chemo radiation David you know is,
is very is with immunotherapy

is also very beneficial.

So we have multiple options.

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,
I try to find ways that I can give immunotherapy to a patient.
Yes, because you give her her expression so much more comment.
Any thoughts on have we target that or why doesn’t EGFR inhibition work for those?
Yeah, we’ve tried that. In fact that was the mark as we worked at an MD Anderson and actually we worked with Jose Bazaga on that many years ago.
We thought it would be EGFR expression and that is helpful. You know, if you’re using an 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, with with with with payloads.

So that might be an 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 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
00:59:32.992 --> 00:59:34.257 strict they’ve they’ve been reused a
00:59:34.257 --> 00:59:35.997 bit but you know it has to have been
00:59:35.997 --> 00:59:37.473 someone who’s had a smoking history.
00:59:37.480 --> 00:59:38.356 So of course it it it,
00:59:38.360 --> 00:59:40.103 it doesn’t take into account any of
00:59:40.103 --> 00:59:41.868 these patients who are the never smokers
00:59:41.868 --> 00:59:44.120 or the light smokers which are the ones
00:59:44.120 --> 00:59:45.720 that have these different mutations.
00:59:45.720 --> 00:59:48.060 Certainly you know looking in in
00:59:48.060 --> 00:59:50.696 the DNA and and and and CTDNAI think
00:59:50.696 --> 00:59:52.360 that’s going to be the way to go.
00:59:52.360 --> 00:59:55.000 We’re already using that for minimal
00:59:55.000 --> 00:59:57.080 residual disease both to determine
00:59:57.080 --> 00:59:59.250 whether or not patients need more therapy
00:59:59.250 --> 01:00:01.033 and 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

screening someone with a history or will we

start looking for tumor DNA,

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

So we need to think about how we’re going to

maybe that’s the way to jump jump forward.

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.