Logon wanna thank everyone for for joining us for Cancer Center grand rounds and we really are very fortunate to have a special guest speaker today. Before I introduce Troy as some of you may have over heard, I alluded to just want to remind everybody that tomorrow at 5:00 o’clock we have a special smile. Oh, town Hall with a guest Speaker, Doctor Ned Sharpless, the director of the National Cancer Institute, too. Provide some comments and answer questions.
As many of you may have seen on Friday, Doctor Sharp offered up his priorities for the NCI for the coming year and I think it would be great to get clarity on what his plans are, how that aligns with our initiatives and interests and to assist in general have him answer our questions.

So without further ado, let me introduce our speaker, who really requires no introduction. Doctor Roy purposes, the Ensign Professor of Medicine and Professor of pharmacology, the chief of medical oncology,
and The Associated Cancer Center

Roy, as you know, is an internationally recognized leader in innovation in the treatment and research of lung cancer. His efforts really over the many years of his career have have really led have changed the landscape of our understanding of the biology and frankly launching new therapies both with respect to targeted therapy and more recently, with immunotherapy. And that work continues with such impact in productivity.
In along,

Roy’s accomplishments span far beyond just his ability to innovate as a researcher and clinician. But also as a leader, having brought the spore to the long program, which now makes it one of the most effective, most impactful thoracic oncology programs on the planet. Roy has beyond that, trained countless leaders globally. And frankly, the influence of his commitment to clinical care, education, and research really can be.
Is beyond measurement so really pleased to have Roy share with us his perspectives on the work and you know the accomplishments he’s had recently and over the years, so Roy, thank you.

Thanks Charlie for that wonderful introduction and thank you Paula and the team here at North Haven where I was seeing patients this morning who sent me up in this wonderful conference room. We’re getting back to some normalcy. 'cause staff are all having lunch.

We put a lunch out today and watching from distant locations so I’m really happy to be here today to give
this grand rounds translational lung Cancer Research at Yale. 10 years in review. And here in my disclosures. So long answer of course is a major problem in cancer. In medicine you can see on the left with the pie chart. Lung cancer is the biggest single piece of that pie you know you can see breast and prostate right there. Of course GI cancers, but the leading cause of cancer death in most countries. 84% of lung cancer is non small cell
lung cancer and more than half present in the advancement of static setting.

NOTE Confidence: 0.842007577419281

That tobacco is the single largest preventable cause of lung cancer and cancer in general and in lung cancer.

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We have actionable genetic mutations, so those are mostly in non smokers.

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But there’s been a great deal of progress and I’m going to talk about that today.

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Well, I went into lung cancer when I was a fellow at the Dana Farber.

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in the mid 90s and this was the status of lung cancer at that time.

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And you might ask, why did I go into the field?

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You can see here’s survival curves
progression free survival curves for patients with lung cancer. This was the top trial at the time that took platinum plus gemcitabine or paclitaxel docetaxel and the bottom line is all of the regiments were about the same. The one year survival 33% median survival only 7.9 months. So if you have a diagnosis of metastatic lung cancer, it wasn’t really that much hope. There were no predictive markers. So why did I go into the field? Well, two reasons I happened
to meet a fellow Tom Fry,

He took me under his wing and said, well, translational research in this field can only be a positive thing.

Give it a try and two, it was really the only job available back then,

so I took it.

Now of course you know the field is very competitive to work in and I'll show you why.

So paradigm shift was clearly needed.

So here you can see the lung cancer mortality,
being made men up top and women
up on the bottom and you can see
51% decline since 1990 mortality.
Now some of that is incident so
you can see the incidence rates
are going down but mortality is
going down in excess of incidents.
So clearly we’re making progress
we’ve seen a new era in lung cancer.
and I’m going to tell you a little
bit about that during this talk.
So really,
we’ve seen a new era in lung cancer.
We had some better chemotherapies.
No doubt they were better.
Then we had bevacizumab Avastin,
Antiangiogenic therapy.

That certainly helped, and then the Genomic Revolution and then hit lung cancer like no other disease, a common disease, and especially in the never relied smokers, actionable mutations were seen. And then you can see all these different mutations that could be targeted with drugs. The era of personalized therapy, though the work that had been done CL and breast cancer transferring very quickly to the large population of lung cancer. And then of course in the last decade alot
00:06:08.829 --> 00:06:11.910 of it LED from here at yell be immunotherapy.

00:06:11.910 --> 00:06:14.376 So I’m going to tell you a little bit about our young spore and the areas where we’ve made progress in lung cancer really mirror what we study in our long sport.

00:06:17.175 --> 00:06:19.541 Whether it be smoking cessation, targeted therapy. Immunotherapy and then I have some future thoughts that I want to share with all of you.

00:06:22.054 --> 00:06:23.639 Whether it be smoking cessation,

00:06:23.640 --> 00:06:25.056 targeted therapy. Immunotherapy and then I have some future thoughts that I want to share with all of you.

00:06:27.447 --> 00:06:29.159 I want to share with all of you.

00:06:30.670 --> 00:06:32.530 have such an amazing team here.

00:06:32.530 --> 00:06:34.778 And remember, it’s all about the team and the people that are working together.

00:06:36.810 --> 00:06:38.034 Everyone from the doctors,

00:06:38.034 --> 00:06:39.870 the nurses to the research scientists,
00:06:39.870 --> 00:06:41.214 the whole Cancer Center.
NOTE Confidence: 0.796012938022614
00:06:41.214 --> 00:06:43.553 So we put Asporin started working on
NOTE Confidence: 0.796012938022614
00:06:43.553 --> 00:06:45.380 this when I arrived here in 2011.
NOTE Confidence: 0.796012938022614
00:06:45.380 --> 00:06:48.125 We were awarded a lung cancer spore in 2015.
NOTE Confidence: 0.796012938022614
00:06:48.130 --> 00:06:49.684 That’s the New Haven Country Club
NOTE Confidence: 0.796012938022614
00:06:49.684 --> 00:06:51.799 where we had a little celebration.
NOTE Confidence: 0.796012938022614
00:06:51.800 --> 00:06:53.636 We renewed this more in 2020.
NOTE Confidence: 0.796012938022614
00:06:53.640 --> 00:06:54.250 We couldn’t,
NOTE Confidence: 0.796012938022614
00:06:54.250 --> 00:06:56.385 of course go to the Country Club,
NOTE Confidence: 0.796012938022614
00:06:56.390 --> 00:06:59.162 but we had a very nice zoom cocktail party.
NOTE Confidence: 0.796012938022614
00:06:59.170 --> 00:07:01.126 C. Charlie Is there with us.
NOTE Confidence: 0.796012938022614
00:07:01.130 --> 00:07:03.080 It was really an amazing thing.
NOTE Confidence: 0.796012938022614
00:07:03.080 --> 00:07:04.880 We’ve now refunded the sport and
NOTE Confidence: 0.796012938022614
00:07:04.880 --> 00:07:07.190 you can see the four major areas
NOTE Confidence: 0.796012938022614
00:07:07.190 --> 00:07:09.272 we started with targeting PD one.
NOTE Confidence: 0.796012938022614
00:07:09.280 --> 00:07:10.255 Obviously with leaping,
targeting, EGFR resistance, smoking cessation, and we had a project with micro RNA with Frank Slack who has since left for Boston. And we have a team and just an amazing team. These are just the leaders of the team. There are so many others that have developmental projects and career developmental projects. But working together to combat this deadly disease, I'm really fortunate to have been able to work with such an amazing group.
you about each of the projects in
brief immunotherapy of advanced lung cancer.
Leaping Scott myself and David Rim targeting
the EGFR pathway in lung adenocarcinoma.
Katie Poletti, Sarah Goldberg, Mark Lemon.
Molecular determinants of lung cancer metastasis and drug regiments
in the central nervous system.
Don when Veronica Chang and Abby Patel and then we haven’t carried
this on to the new sport,
but we’re continuing the work personalized
intervention project for tobacco treatment.
Probably the most important thing
I trained with Weinke Hung and if
00:08:11.286 --> 00:08:12.120 we prevent cancer,

00:08:12.120 --> 00:08:14.514 will actually save many more lives

00:08:14.514 --> 00:08:16.856 in any other therapies ever talk

00:08:16.856 --> 00:08:18.208 to you about today?

00:08:18.210 --> 00:08:20.214 And one important thing is we

00:08:20.214 --> 00:08:22.670 develop that new project on the left

00:08:22.670 --> 00:08:24.430 from 2 developments or research

00:08:24.430 --> 00:08:26.380 projects over the last six years.

00:08:26.380 --> 00:08:28.162 So here again are the projects

00:08:28.162 --> 00:08:29.053 in the leaders.

00:08:29.060 --> 00:08:31.444 I just want to point out the cores.

00:08:31.450 --> 00:08:33.529 The amazing thing about aspor other cores.

00:08:33.530 --> 00:08:35.616 I’m very fortunate to have a partner,

00:08:35.620 --> 00:08:37.601 an Ed captain who I’ve been working

00:08:37.601 --> 00:08:39.735 with now for six years and has

00:08:39.746 --> 00:08:41.485 with the project.

00:08:41.485 --> 00:08:43.741 That’s why we’re always interested in new ideas.
helped to bring the team together,

Very successful.

They had an export,

was just funded in large part to it.

His efforts working with Barbara

statistics and Bioinformatics.

I won’t say much about it because their work

is in every project I talked about today.

But Steve Mahan Usau he can’t

do anything without statistics.

And I will highlight a little

bit of by open specimen.

Core pathology is key tissue banks,
NOTE Confidence: 0.793626368045807
00:09:06.592 --> 00:09:08.060 in career enhancement program.
NOTE Confidence: 0.793626368045807
00:09:08.060 --> 00:09:09.380 I thank Karen Anderson,
NOTE Confidence: 0.793626368045807
00:09:09.380 --> 00:09:11.710 Pat Larusso and Harriet Kluger for this.
NOTE Confidence: 0.793626368045807
00:09:11.710 --> 00:09:12.366 50 projects.
NOTE Confidence: 0.793626368045807
00:09:12.366 --> 00:09:13.022 Young investigators.
NOTE Confidence: 0.793626368045807
00:09:13.022 --> 00:09:14.990 People who weren’t working in lung
NOTE Confidence: 0.793626368045807
00:09:15.046 --> 00:09:16.686 cancer in the developmental field.
NOTE Confidence: 0.793626368045807
00:09:16.690 --> 00:09:18.958 Now we’re working on lung cancer with
NOTE Confidence: 0.793626368045807
00:09:18.958 --> 00:09:21.338 many muara ones and other team grants.
NOTE Confidence: 0.793626368045807
00:09:21.340 --> 00:09:24.268 So it really has created a whole culture
NOTE Confidence: 0.793626368045807
NOTE Confidence: 0.793626368045807
00:09:26.910 --> 00:09:28.878 I don’t want to forget the clinic I’m
NOTE Confidence: 0.793626368045807
00:09:28.878 --> 00:09:31.229 in the clinic I’m in North Haven today.
NOTE Confidence: 0.793626368045807
00:09:31.230 --> 00:09:33.120 He can’t do this without the clinic.
NOTE Confidence: 0.793626368045807
00:09:33.120 --> 00:09:34.752 It’s gotta be a seamless transition
NOTE Confidence: 0.793626368045807
and I won’t have too much time to talk about the top program today.

Maybe another grand rounds, but we had to retreat back in 2012 and then you can see.

And this is just as we both care centers in the care centers are critical to this. I’m out of care center patients are being seen here with lung cancer.

Tissue specimens are going back to Cedar St. This is what we need. The top team?

Linton Uian Frank form top. 1520 years ago, it’s tremendous user clinical trials director Roy Decker.

This is our most recent retreat
00:10:01.712 --> 00:10:02.840 at the Business School,
00:10:02.840 --> 00:10:05.096 and here I am at the very first.
00:10:05.100 --> 00:10:06.750 We talking about a truckload battle
00:10:06.750 --> 00:10:08.760 that I brought over from MD Anderson.
00:10:08.760 --> 00:10:11.728 We put 40 patients on this drive with
00:10:11.728 --> 00:10:14.328 biopsies and help get this war going.
00:10:14.330 --> 00:10:16.000 So what about smoking cessation?
00:10:16.000 --> 00:10:16.334 Well,
00:10:16.334 --> 00:10:17.670 the health consequences of
00:10:17.670 --> 00:10:19.006 smoking are just enormous.
00:10:19.010 --> 00:10:21.320 80 to 90 different toxins in tobacco
00:10:21.320 --> 00:10:23.373 smoke and you know the decrease
00:10:23.373 --> 00:10:25.683 in risk and lung cancer is seen.
00:10:25.690 --> 00:10:27.360 Usually takes about five years,
00:10:27.360 --> 00:10:28.974 but you never reached the baseline
and a sensation after diagnosis.

clearly improves treatment tolerance,

So we have a very concerted effort on smoking cessation here.

And it was one of the projects of the score.

Certainly we want to do a lot of work with policy.

I’ve been involved with the ACR

we’ve now gotten into work with the cigarettes you can see on the bottom
	right this to chytra with me at

in Washington, along with Durbin,

an E cigarette briefing.
We need to stop the initiation of tobacco use. We worry about the E cigarettes and whether patients and people will start to smoke tobacco cigarettes, smoking rates still remain about 18%, but why is it so important? Because it's higher in our community. Because we have community, that's that's a more diverse community that has more long-term smokers. So look at the right for a section a second, you can see that we did a study personalized intervention project. I could see 42% of
our people on that study where unemployed or on disability.

You can see the large number of minority patients that were on this trial.

So this is so vital for our community.

So Ben told. Along with the team and Susan main work with us before she came and Brenda Cartmel created a trial where we had patients.

Our target was 276.

We enrolled about 200 and we’re analyzing the data now and they either had standard cessation or they had cessation treatment with personalized messaging.

Gained frame messaging.
What is that for?

Anyone who’s traveled?

We haven’t done that too much recently

and you’ve seen those cigarette

cartoons in the airports that have

their really horrible looking pictures.

That’s negative non-gained frame messaging,

but more positive messages

which we actually translated.

Into several languages were used to see

if that would help patients to stop

smoking and then to keep them from smoking.

We had a biomarker biofeedback method

that Susan main developed looking at

skin carotenoids which actually got
higher in patients who stop smoking and patients could see their number. So this trials under analysis right now. But you can see the team that came together to do this and now of course Lisa for Cheeto who leads that effort here at Yale. Now with the team doing a great job, we brought that group to Medical University of South Carolina. Here’s the team there. We would go out to different. Forums and we talk about our work. You can see it was only possible because of the work of linen at the VA, and Alyssa Roy Tobacco treatment groups
at yeah and all the different groups.

And there I am doing the Roman spectroscopy wasn’t too difficult procedure,

but you know the real thing is it got us into the community.

We’re continuing this work.

We spoke with a caring ambassador program.

There’s teacher Johnson and that program and we were able to work with them to get this out there.

We were able to get grand Beth Jones. Tina and myself,

a grant from BMS to go out and do more of this work in the community and here we are just last week.
Giving masks at Fair Haven clinic

as an and the message of sensation

so smoking cessation very important.

What about targeted therapy?

Well,

I got into this about 1990 seven

when I was first at MD Anderson

and I was called into the office

with John Mendelsohn and kihon.

I talked to them about you know,

some targeted therapy and I've been

I said,

how would you like to lead this effort

and it says sure,

Fortunately there were trials,

both in-house trials and industry
00:13:51.485 --> 00:13:52.817 trials at the time.
00:13:52.820 --> 00:13:55.655 And there’s a drug called ZD 1839 and we
00:13:55.655 --> 00:13:58.486 did the first phase one trial of that.
00:13:58.490 --> 00:13:59.195 And it works.
00:13:59.195 --> 00:14:00.840 Now you can see I ended up
00:14:00.904 --> 00:14:02.420 working with my future
00:14:02.420 --> 00:14:04.315 collaborator and friend Pat Aruiso.
00:14:04.320 --> 00:14:06.957 We met in 1998 working on this trial and
00:14:06.957 --> 00:14:08.929 patients with lung cancer like this,
00:14:08.930 --> 00:14:11.034 he would have had less than six months
00:14:11.034 --> 00:14:13.229 to live had these wonderful results.
00:14:13.230 --> 00:14:14.940 So this was the dawn of
00:14:14.940 --> 00:14:16.600 EGFR therapy in lung cancer,
00:14:16.600 --> 00:14:19.435 and they have a friendship and partnership
00:14:19.435 --> 00:14:22.050 with Pat that’s lasted to this day.
So of course I’m not going to go through everything in this short talk, but through those works, the EGFR Mutation was discovered. Of course, Tom are former director was very involved in that and Bruce Johnson and Pasion in the group Boston. We actually got to a point in the mid 2000s where patients could live. Here’s a patient with metastatic lung cancer who is living with cancer, taking oral EGFR inhibitor each day, some skin issues, some mild diarrhea. Tara Parker, Pope wrote this article in 2003. Why curing your cancer may not
00:14:55.442 --> 00:14:56.710 be the best idea.
00:14:56.710 --> 00:14:58.894 The idea was lung cancers become a disease like hypertension or diabetes.
00:14:58.894 --> 00:15:00.509 The problem with the targeted therapy for EGFR is no one's really ever cured.
00:15:00.510 --> 00:15:02.328 Resistance will ultimately develop well here.
00:15:02.328 --> 00:15:04.950 It's a little bit about that.
00:15:04.950 --> 00:15:06.846 So we started in 1997.
00:15:06.850 --> 00:15:08.758 The second line therapies with the different nib or laugh and have some of those agents.
00:15:08.760 --> 00:15:10.340 The mutations were discovered right around in here.
00:15:10.340 --> 00:15:11.980 The decision was made to give these drugs only to patients with mutations.
So then we started to use these drugs in the frontline setting. And then we had new generation drugs and a new generation drive was Aston Martin. If this drug being less toxic because it was targeted just to EGFR Mutant Receptor, the other drugs targeted all EGFR receptor, so it had fewer side effects. And it also was developed to go to the brain to the CNS. So with this drug we had better therapy in the metastatic setting. When I’m going to tell you about now is something that I got involved with right around this time with the team to take the drug to Azure and therapy,
take it to earlier disease.

And I mentioned Tom Fry and the one thing he always would tell me is bring your drugs to the earliest most curable setting. Well, we did that.

So in early lung cancer. Let’s say someone to find themselves to have an early lesion in the lung, perhaps a few local lymph nodes or even some mediastinal lymph nodes. The chance of them being cured with surgery is reasonable, but it’s not. It’s not good enough, so we would cut these damn boffa Frank.
better back in the team would cut these out.

But then we might even give acumen chemotherapy. Which maybe has a 5% or so improvement in outcome but still in stage one disease. The earliest disease you know only 60 to 70% of patients are cured. Stage two patients only 47 to 55% and it stage three only 38%. So if you have these patients and they have each year for mutations and it’s only 10 to 15% of patients in the US, about 20 to 30 in Asia but still enough lung cancer patients that if you could find these patients and give him something else,
it could make a big difference.

Well here comes the Adora trial. I was very fortunate to be one of the people who designed this along with Masahiro Suboi from Japan and Ylang Wu in China. Of course, EGFR mutations being much more prevalent there. We’ve been working on this for almost a decade, so here we took patients who quit completely respected stage 1B, two or three. A disease with or without active chemotherapy.
So patients could receive their standard care and you can see they all had recently good performance status. They all had rain. Imaging they had the two most common types of each year for mutations in Exon 19 or 21, and they could have actually been therapy. They started within 10 weeks if they did not have action in chemo and within 26 weeks if they did. There were stratified by their stage. The trial is about an equal number of stage one B2 and three a weather each year from mutation status 19 or L858R21 or their
race Asian versus non radiation. About 1/3 of the patients came were non Asian, 2/3 Asian and a very simple trial and you know simple trouser. Sometimes the best answer merchant 80 milligrams orally once a day versus placebo. I’m often asked how could you do a pussybow because there was no other standard of care. We just waited for these tumors to come back. Coding insights like the brain delivering 682 patients on trial. The planned duration of treatment is 3 years, so they got three years of
treatment and they stopped.

If they record and the follow up you can see every 12 weeks for the first few years and then every 24 weeks.

The primary endpoint of this trial was disease free survival, so surviving without recurrence for a hazard ratio of 0.7. So for 30% improvement.

The secondary endpoint was disease free survival in the overall population with source continuing and then 234 and five year landmarks. Overall survival, safety and quality of life.
I was not expecting to be presenting these data this year. It was a plenary talk at ASCO. I gotta call during Passover. I guess it was on Good Friday. So around April 10th or so the trial had been underlined. Because the independent data monitoring committee unblinded study early. Do the Efficacy they were doing a safety review, but they saw that the Efficacy was so good, which is almost unheard of and they did an unplanned interim analysis and
the study had completed enrollment.
All patients ran for at least one year,
so they decided to unblind the trial.

So I got that call and by the next week we were already preparing an Astro presentation.
Why? Because these were the data.
Remember, I told you that was powered for a 30% improvement,
but look here on the left.
These are patients with stage two and three a disease.
The primary population.
This is a disease free survival for patients on the astroneer can have the pill versus those on the placebo.
The hazard ratio here is 0.1 seven.
That means there’s an 83% improvement. Again, we expected that this drug would work, but with this much magnitude. It was just incredible. And then when you add in the 1B patients, patients who would have a good prognosis to begin with, I told you half of those were cured. The hazard ratio still 0.2 zero 80% improvement. So these these data were quite impressive to all of us and that’s why it was presented so quickly. This is a forest part, which is often done in these types of trials.
Here you can see the unity line, anything to the left favors the App Store merchant and they think of the right favors. The placebo. You can see everything is to the left, whether it be sex, age, former smokers still did well whether they were Asian or non Asian. The race, the stage I told you, equal numbers and all three. Even the early stage ones still make it across the line and then each information status didn’t matter. And of course. Whether they got acumen chemotherapy
enough or not didn’t seem to make a difference as well, so all this was positive, really, really very positive trial. 

So where are we at with this? Just to give it in perspective, I’m sure many of you want to know what about overall survival. We won’t have that for a couple of years. The trials continuing on, and that will be filed. But right now we want to know the local versus disease recurrence, including the sites of recurrence I mentioned the brain,
the liver and the bone.

And actually I this is a nice. Picture from an Chang and an article she wrote with Johann Mascia number years ago, but that’s the thing.

Even without the survival result, our patients are occurring in these very sensitive sites.

What were the subsequent therapies in one of the quality of life? All this is still percolating and will present it shortly.

In fact, I’d like to just say a word about this.

The idea that we’ve taken targeted therapy, and we’ve added it to our best surgery,
an Azure in therapy.

And now we’re seeing better outcomes for patients.

And I can’t help but think about my late mentor, Isaiah Fiddler.

He digester earlier this year.

He would always talk about that biology is the foundation of therapy and that’s what we’ve done with your trial.

Now I wish I could tell you more,

so I hinted to you about the brain Mets.

I’ll tell you that it’s good

that there’s going to be an embargoed presentation at Esmo this
Saturday at 12:30 our time and a paper coming out in the Journal.

I'm not supposed to talk about it, but in a Journal that the Mass Medical Society publishes.

So this will be out. So this will be out.

You'll be able to see it by Saturday.

So where are we at with this now?

Now we have to even add in more science.

So now we have an alliance with Astra Zeneca that Patton Russo and I were able to develop.

And you can see we're working with their tool compounds with them on all the different questions I just talked about brain metastases,
resistance mechanisms and you can see that here is our summit meeting exactly a year ago, but now we just had a call with them yesterday morning. And now with Katie plenty and on when an hobby re biopsy study and analysis. Cell free DNA from Adora to understand mechanisms of resistance we need to use this trial and the samples for the patients who are still on a trial to understand when do they develop resistance in their blood. When can we measure the resistant clones? How can we determine how long to
treat when to start new therapies?

So all of this is very exciting and really speaks to how Science has gone into the clinic and how we’ve evolved over 20 years to really make a difference in lung cancer with these targeted agents.

You can see here’s project two so Katie Poletti leads us along with the rest of the team. And you can see here’s project two of the spore so Katie Poletti leads us along with the rest of the team.

You’ll see in a moment, so we actually have programs here to optimize approaches to counter on target.

EGFR dependent mechanisms of resistance so you can see up here we have mice when when patients recur,
we get tumor and they go into the mouse and we have mice that are resistant to these drugs and we can try to look at new therapies and correlate that with patient data. Some of these are genetically engineered mice and then we can look at vulnerabilities of T eeki Resistance. In two minutes without on target. Here for resistance, there are other mechanisms and we have clinical trials and studies to look to understand why the patients would become resistant, because as good as we are,
we’re going to see this resistant merge. So we have to stay one step ahead of this. And that’s what Katie and the team are doing. So here’s that wonderful project team I mentioned Katie working with Sarah Goldberg and Mark Lemon Collaborative Group. You know each other projects has its own team that meets on a regular basis. Here’s the list, samples from the clinic PDX models, genetic models, drugs in collaboration with industry investigator initiated trials. That’s the way we’re going.
to continue to make progress in lung cancer. And you can see productivity. No problem with this group.

You can see a number of key publications, allele specific patterns of resistant resistance approaches to overcome and prevent the emergence of resistance.

So it’s taking time to develop all this and molecular modeling to understand these mechanisms. So really really talented group working together.
And then, of course brain metastases. We have a separate team doing that. We have done along with Veronica Chang, neurosurgeon done being a basic scientist and Abby patellar radiation oncologist. That translation researcher, so there trying to look at mediators of CNS metastasis to lung cancer. We were getting CSF samples from patients who have lung metastases. To understand what’s going on in the CSF in the cerebral spinal fluid. And then we’re going to understand adaptive mechanisms of tumor dissemination and drug resistance in the brain. A number of key papers already published,
and then we're going to use this CSF to identify biomarkers and genetic drivers of metastases. So all of this already on going again, the lab, the clinic interspersed together. So with that on now focused on immunotherapy. So if all we have already talked about was not enough, amino therapy is perhaps even more powerful tool if we can learn how to harness it. Well, I've been at yell since 2011. This is the patient from 2010, so one of the reasons I was attracted to come here as I met with Scott and
Mario and they told me about this thing. I was at MD Anderson. We didn’t know anything about it. We weren’t doing any immunotherapy work back then and Scott showed me some X Rays and I said wow and really, you know, initiated this clinical field. Patients with refractory lung cancer. This is Maureen. This is a center point so I’m able to show her picture. But here we have a patient with refractory disease three times refractory squamous lung cancer.
Very few of them Lego markers would be there. There would be very little targeted therapy for this type of patient, but look at this response but more important than this amazing response is now 10 years later, she’s still alive and well. So we actually because of the work we’ve done subsequently, Bob Sherwin and teacher Johnson put us in for Team Science Award at the Association for clinical and Translational Science and loan. Behold, we got it. You know,
a little bit of money that we split,

but you can see you know these are just a few of the many people at captain.

Of course, Harriet Mario snow.

And then of course sleeping my good friend and collaborator,

a team working on this,

and I'm going to show you more recent work from this team.

So I'm going to ask the question and I don't know if it's the beta is watching if this weather regular grand rounds.

I looked on the right and I'd seen there, but he's inspired me for many years.

Can we cure metastatic lung cancer?
A question you wouldn’t even asked 20 years ago.

Of course, not even ten years ago, but I’d like to ask that question today.

And then we’ll talk about it at the very end of my talk.

I tried to read up a little bit.

What’s the definition of cure to restore health to bring about recovery from?

Look up at Hippocrates.

Cure sometimes.

Treat often comfort always,

but this is the most inspiring book we,

of course, had a grand rounds with

Vince and Elizabeth a few years ago.
The way that they cured, shouted Lymphoma and adult lymphomas. Can we do that in lung cancer? Remember, lung cancer is a little bit different. Disease also affects people who are older and more comorbidities, but keep that question in mind. ’cause I’m going to ask you again in about 20 minutes. Well, lung cancer therapies just evolve so quickly, so this first round up here keynote, one call later, was the of this. He’s an author on the New England Journal of Medicine Paper.
We had this in our phase one clinic. You'll still bump into patients in the Hall who were on this trial 678 years ago who are alive and well. This was Pember Lizum app. It was given to all comers in a number of different lung cancer types, but subsequently the biomarker was shown to predict who did a bit better PDL 1. I got involved. This is a trial Iran keynote 10. This resulted in Pember Lizum app getting licensed in the second line setting. We actually showed that a two doses when you use pembrolizumab versus docetaxel.
00:29:14.290 --> 00:29:15.698 either selecting for all
NOTE Confidence: 0.832143545150757

00:29:15.698 --> 00:29:17.834 patients with 1% or more PDL.
NOTE Confidence: 0.832143545150757

00:29:17.834 --> 00:29:20.999 One or patients with high PD L1 at 50%.
NOTE Confidence: 0.832143545150757

00:29:21.000 --> 00:29:23.720 We saw a significant benefit.
NOTE Confidence: 0.832143545150757

00:29:23.720 --> 00:29:24.614 Then of course,
NOTE Confidence: 0.832143545150757

00:29:24.614 --> 00:29:26.104 from this trout the biomarker
NOTE Confidence: 0.832143545150757

00:29:26.104 --> 00:29:27.479 was used in Frontline.
NOTE Confidence: 0.832143545150757

NOTE Confidence: 0.832143545150757

00:29:28.194 --> 00:29:29.265 Parallelism addresses chemotherapy
NOTE Confidence: 0.832143545150757

00:29:29.265 --> 00:29:31.890 the five year data for this will also
NOTE Confidence: 0.832143545150757

00:29:31.890 --> 00:29:33.731 be presented this this week in Ezmo.
NOTE Confidence: 0.832143545150757

00:29:33.740 --> 00:29:34.318 Trust me,
NOTE Confidence: 0.832143545150757

00:29:34.318 --> 00:29:36.052 it looks pretty good and then
NOTE Confidence: 0.832143545150757

00:29:36.052 --> 00:29:38.117 you can see the Pacific Travel.
NOTE Confidence: 0.832143545150757

00:29:38.120 --> 00:29:40.255 This is even this is again sort
NOTE Confidence: 0.832143545150757

00:29:40.255 --> 00:29:41.869 of like with the Dora.
This is stage three lung cancer using their vile map and you can see improvement in survival after chemo radiation. But I wanted to show some of our own data, so here’s Scott’s trial. Scott and Mario. This is where Maureen was. She was on this trial and look at the actuarial five year survival from that first trial. And if all mad here at Yeah 16% and you know what Scott knows, everyone of those patients who is alive and he’s got their samples and he’s analyzing them right now.
But you know, it’s really all about the tail. If you look at this survival curve now, we gotta do better here. We lose a lot of patients early on when they get to this tale. Is it as good? I look at this with Mario. Today is it as good as Melanoma? Maybe not quite it, still earlier too. And this is a disease you know of. People who smoke and have other mutations, but you know what? It’s looking pretty darn good to me. And then of course, you know you’ve got a credit Harriet, for her constant mentor ship.
We know working with Sarah early on in her tenure here and Veronica again, our neurosurgeon. And they actually said, why do we have to exclude patients with brain Mets from these trials? That’s not the real world. So here’s a patient with lung cancer with brain Mets was treated with Pembrolizumab, and those brain Mets went away. This was an investigator initiated trial because we’re doing some of the keynote trials,
we were able to get a relationship with Merck. It helped us to get this drug in lung and Melanoma. They collaborated together and what this is showing as this is a wonderful plot. Each of these points below the line is a patient who responded, but what you can see is the response in the brain and the lung looked to be about the same. So now real world trials and neutrals are allowing patients with brain Mets to get parallelism at ’cause it apparently works across the blood brain barrier.
That’s very important.

So where are we right now?

Again, I only have an hour,

but here’s a nice slide made by hand Chen.

She wrote a beautiful review in nature

reviews clinical oncology earlier this year,

and basically we look at squamous

or nonsquamous lung cancer.

And we look at PDL one expression

and we have we have therapies for

patients who have less than 1% PDL,

one to 49% pdo one or greater

than 50% PDL 1,

and that’s sort of the way things
00:31:55.971 --> 00:31:58.079 are assorted right now and approved
NOTE Confidence: 0.8449826836586
00:31:58.079 --> 00:32:00.549 as a single agent are two drugs.
NOTE Confidence: 0.8449826836586
00:32:00.550 --> 00:32:02.382 Humble is a map and a Texel is
NOTE Confidence: 0.8449826836586
00:32:02.382 --> 00:32:04.461 a map where you can give these
NOTE Confidence: 0.8449826836586
00:32:04.461 --> 00:32:06.280 to patients with high PD L1.
NOTE Confidence: 0.8449826836586
00:32:06.280 --> 00:32:07.714 They don’t even need chemotherapy just
NOTE Confidence: 0.8449826836586
00:32:07.714 --> 00:32:09.560 for the sake of today’s discussion,
NOTE Confidence: 0.8449826836586
00:32:09.560 --> 00:32:11.528 I’m going to talk about a Tesla is
NOTE Confidence: 0.8449826836586
00:32:11.528 --> 00:32:13.633 a mad ’cause Yale has had a very
NOTE Confidence: 0.8449826836586
00:32:13.633 --> 00:32:15.335 big part in its development and
NOTE Confidence: 0.8449826836586
00:32:15.335 --> 00:32:17.743 I’m going to show you how we took
NOTE Confidence: 0.8449826836586
00:32:17.750 --> 00:32:20.150 this drug all the way from the very
NOTE Confidence: 0.8449826836586
00:32:20.150 --> 00:32:22.397 first in human dose now to face.
NOTE Confidence: 0.8449826836586
00:32:22.400 --> 00:32:24.856 So about 2012 you know Paul and I
NOTE Confidence: 0.8449826836586
00:32:24.856 --> 00:32:26.660 were approached by by IRA Mellman.
NOTE Confidence: 0.8449826836586
00:32:26.660 --> 00:32:29.092 Some of you might know, IRA and IRA,
of course, had an affinity for Yale.

He had, I believe he was the scientific director of the Cancer Center for many years, and I actually knew him 'cause I took his course as a Rockefeller graduate student.

So I've ever called and they said, would you like to be involved in this trial? And he said, yes, we said, can we do a trial with your new drug test Alyssa Map, which is a PD L1 inhibitor. That PD, one PD, L1 or can we include biopsies because we like to do biopsies.
We had that working and we want to understand the mechanism and they actually said sure so working closely with Scott and Petrol Act was very involved. They had amazing data and bladder cancer and with Paul and then Pat. When she arrived we did this trial and we treated almost 30 patients, maybe 35 here. And yeah and we got biopsy. And here's a patient with multiple lung metastases who had a complete response. And in this patient we gotta buy a seat recruitment and biopsy where they went off treatment. And that's very helpful because you could look at CD 8 cells and these are T
cells and you can see before treatment there's not very much CD sales here. But after treatment the T cells all swarm into the tumor. That's an example of the adaptive immune response, so we actually in our publication and from this work described what was happening at the level of the tumor in patients who are getting these drugs even more incredible. This RNA chip that we did. Again, working with Iran. Danshen Steve Odeon Farberware involved. We had a collaborative team as many
00:33:58.694 --> 00:34:00.602 of these clinical trials are but
NOTE Confidence: 0.798537015914917
00:34:00.602 --> 00:34:02.890 you can see pre and post on this.
NOTE Confidence: 0.798537015914917
00:34:02.890 --> 00:34:04.829 The Green is pretty yellow is post
NOTE Confidence: 0.798537015914917
00:34:04.829 --> 00:34:07.074 so you can see Granzyme granzyme is
NOTE Confidence: 0.798537015914917
00:34:07.074 --> 00:34:09.484 an enzyme that’s made by cells having
NOTE Confidence: 0.798537015914917
00:34:09.484 --> 00:34:11.682 an active immune response so you can
NOTE Confidence: 0.798537015914917
00:34:11.682 --> 00:34:14.188 see the grandson goes up in the post.
NOTE Confidence: 0.798537015914917
00:34:14.190 --> 00:34:16.318 This is a patient having good immune
NOTE Confidence: 0.798537015914917
00:34:16.318 --> 00:34:18.026 response on here is perforant
NOTE Confidence: 0.798537015914917
00:34:18.026 --> 00:34:19.861 preference thing about Perforant as
NOTE Confidence: 0.798537015914917
00:34:19.861 --> 00:34:22.315 being an enzyme that makes a hole in
NOTE Confidence: 0.798537015914917
00:34:22.315 --> 00:34:24.492 the tumor cell and cause it to burst.
NOTE Confidence: 0.798537015914917
00:34:24.492 --> 00:34:26.256 Looking at the hyperforin that you
NOTE Confidence: 0.798537015914917
00:34:26.256 --> 00:34:28.348 see after treatment versus before,
NOTE Confidence: 0.798537015914917
00:34:28.350 --> 00:34:30.702 so we defined in this the adaptive
NOTE Confidence: 0.798537015914917
00:34:30.702 --> 00:34:31.710 active immune response.
This was 20% of the patients keep that number in mind, but most of the patients did not respond, so we also had profiles of Nonresponders. So here are three different profiles of non respondents, again with CDA we had one group called immune ignorance. These are patients with no T cells to begin with and no T cells to be at the end. The tumor just laughs at what we're doing. We call this the immune desert. Then you have the non functional immune response. We can see a good number of
cytotoxic T cells,
maybe get a little bit of an increase.
It’s in the paper.
I don’t have time to show it to you with
that immune ship would be negative.
No activation of the T cells.
You don’t send it.
See anything going up and then
we have the immune excluded.
This is very interesting where the
T cells don’t get to the tumor and
this is something we’re very actively
studying in the lab.
How can we get these T cells
to the tumor because of their
interact with the tumor and within?
They're not going to activate, so we understood the patterns of resistance. Now let’s do something about it. Well, we get a great deal of work with the Tassel is a might Academy licensed in the second line setting. You’ll see patients around our center who are benefiting from this. It’s just amazing. So then we’re off for the opportunity to lead the phase three trial using the drug in the frontline setting and we said sure so here you can see this trial chemotherapy naive PDL.
one selected patients with stage

four non small cell lung cancer,

either squamous or nonsquamous.

So untreated patients

We used a little bit of a

Based on the work we had

we thought it would be important to

look at PDL one both in the tumor

PDL one in the immune cells more than 10%.

So we call that TC three IC 3.

We use that in this.

In this study we also use a

slightly different antibody.
I’ll get to that in a moment, but it’s a pretty simple design at
TES Alisimam versus chemotherapy.
Maintenance of Texel is a map versus maintenance chemotherapy.
Endpoint being survival.
Well, here is the result in.
These data are now impressive, though not too long from now.
You can see the curves.
Cross definitely tells us we could do a little bit better with our biomarker,
but here’s the patients who had the high PD-L1 and got the test losing Matt here.
The patients who got the control chemotherapy have a ratio is 0.59 and these data will be followed out more. But again an incredible result. Single agent immunotherapy versus chemotherapy. We also then looked at this in this paper with other markers, so these are two. Here’s the SP 142 which is the market we used for this study. It’s the one that’s used in breast cancer. Is the antibody against PDL one. And then here you can see there are more commonly used to see three ’cause I believe what we
run at least used to run it. Yeah the results with the same slightly different populations.

I won’t get into this today but this trial allowed us to sort of develop some of the biomarker comparisons.

But even more interesting,

I wanted to show this just one slide and again the full report will be out soon.

This was already presented at Esmo, but what you can see is we looked at tumor mutational burden,

the number of vacations for megabase
using the foundation medicine platform
and what you can see is here's another one of those forest plots.
Here's all patients with any PDL one expression, but you can see that when you took patients with a blood based tumor mutational burden, you see a progressive.
Increase in referee survival as you go up in the number of mutations per megabase.
Why is this important?
Predict that someday will use this as a biomarker, perhaps in Association with other biomarkers in in this setting.
Well, what about biomarkers developed at Yale and mechanisms of resistance?
Again, I'm giving an overview today, but you know, so fortunate to have such an amazing team. These are two papers with Scott's first author, but when was led through Katie's lab and was led through Kurt slab just really seminal results. So and I have to credit Rick Lifton. We used to meet with Rick and work with him over at his lab so we had a great team working together so we actually sequenced patients at resistance.
found that those tumors that were resistant had lost beta, two microglobulin and a sexual component of M HC One. So if you know that these are these patients can’t get anymore PD one PD L1, they need other ways of activating the immune system. This is a work in progress, using quantitative immune fluorescence. Had a wonderful study with Scott and cancer discovery and the rest of the team, but they look at different combinations of Biomarkers. Group AB&C. So what this group is?
These are patients that have low T cells and very little. These are patients that have low T cells and these are patients. These two groups that have a lot of T cells. But then he looked at the characteristics of the T cells. These T cells had low granzyme K67 and located at 67. So we’re sort of exhausted and these details you can see by the white. They had high K67 and high granzyme and lo and behold, he showed that that group that had the low chaos 67 and a low granzyme.
They did the best small numbers, but we’re now using our stand up for cancer alliance to validate this more, but it shows that you can identify a group of patients who probably had more ability to respond to immunotherapy biomarkers. Very exciting, this work continues.

I just point that out now, what about resistance? So we have to understand resistance better. This is work from David Rim. He now leads among group at NYU and what
00:40:32.210 --> 00:40:34.855 you can see is we actually took 450
00:40:34.855 --> 00:40:37.473 samples from our archive here at Yale.
00:40:37.480 --> 00:40:40.192 When I told you pathology is key and
00:40:40.192 --> 00:40:42.538 we actually found that only 17% of
00:40:42.538 --> 00:40:44.522 the tumors at high PD L1 and hide
00:40:44.522 --> 00:40:46.758 tumor infiltrating lymphocytes,
00:40:46.760 --> 00:40:49.238 the same 1720%. I’ve been telling you.
00:40:49.240 --> 00:40:50.128 Do real well,
00:40:50.128 --> 00:40:52.108 but here’s 26% of the tumors that
00:40:52.108 --> 00:40:54.379 have a lot of PDL one have sorry
00:40:54.379 --> 00:40:56.659 they have a lot of chill but no
00:40:56.733 --> 00:40:58.647 PDL one so it doesn’t matter
00:40:58.647 --> 00:41:00.821 how much you block PDL 1 here,
00:41:00.821 --> 00:41:02.306 it’s not going to matter,
00:41:02.310 --> 00:41:03.935 but perhaps there are other
00:41:03.935 --> 00:41:05.125
checkpoints in play and then

you can see type one and four.

These are tumors where there

so it doesn’t matter how much

you play around with these

immune checkpoint inhibitors,

we have to inflamed them first so we call 1,

three and four off target.

Target missing resistance and type

one is the on target resistance.

Let me talk about that first.

Even when you give immunotherapy

to these patients,

they still only respond 30-40% of the time,

so something else is going
NOTE Confidence: 0.808094799518585
00:41:30.116 --> 00:41:32.198 on in the macro environment.
NOTE Confidence: 0.808094799518585
00:41:32.200 --> 00:41:33.151 Well known, behold,
NOTE Confidence: 0.808094799518585
00:41:33.151 --> 00:41:34.736 we have David Rahman team
NOTE Confidence: 0.808094799518585
00:41:34.736 --> 00:41:36.061 quantitative mean for essence
NOTE Confidence: 0.808094799518585
00:41:36.061 --> 00:41:37.646 lovely paper recently looking at
NOTE Confidence: 0.808094799518585
00:41:37.646 --> 00:41:39.260 Co localization in macrophages.
NOTE Confidence: 0.808094799518585
00:41:39.260 --> 00:41:41.618 The macrophages are going to be
NOTE Confidence: 0.808094799518585
00:41:41.618 --> 00:41:43.190 important to micro environment
NOTE Confidence: 0.808094799518585
00:41:43.254 --> 00:41:45.029 and outcome looking at markers
NOTE Confidence: 0.808094799518585
00:41:45.029 --> 00:41:47.115 of PDL one and macrophage this
NOTE Confidence: 0.808094799518585
00:41:47.115 --> 00:41:49.091 is what we need to do more of
NOTE Confidence: 0.808094799518585
00:41:49.091 --> 00:41:51.030 like not just these two markers
NOTE Confidence: 0.808094799518585
00:41:51.030 --> 00:41:53.243 that markers in other cell types
NOTE Confidence: 0.808094799518585
00:41:53.243 --> 00:41:55.079 in the tumor microenvironment.
NOTE Confidence: 0.808094799518585
00:41:55.080 --> 00:41:57.816 And we had some extra money on the store.
NOTE Confidence: 0.808094799518585
We still need more money Charlie,

NOTE Confidence: 0.808094799518585

but we just had a little bit

NOTE Confidence: 0.808094799518585

of extra surplus last year.

NOTE Confidence: 0.808094799518585

So what we did is we put it into

NOTE Confidence: 0.808094799518585

tissue microarray with some of the

NOTE Confidence: 0.808094799518585

responders nonresponders very valuable

NOTE Confidence: 0.808094799518585

so we can test different biomarkers now.

NOTE Confidence: 0.808094799518585

And I think they've been in his

NOTE Confidence: 0.808094799518585

group for their complete innovation.

NOTE Confidence: 0.808094799518585

And you can see the rim lab,

NOTE Confidence: 0.808094799518585

just just a wonderful lab.

NOTE Confidence: 0.808094799518585

The only problem is David is

NOTE Confidence: 0.808094799518585

so good he is now part of it.

NOTE Confidence: 0.808094799518585

Had an export of course he’s leading

NOTE Confidence: 0.808094799518585

breast cancer for many years.

NOTE Confidence: 0.808094799518585

We need many more groups like this
00:42:27.357 --> 00:42:29.219 at the Cancer Center and an ocean.
00:42:29.220 --> 00:42:30.756 Lou is very supportive of that.
00:42:30.760 --> 00:42:32.566 This pathology group is just good key.
00:42:32.570 --> 00:42:34.118 But what about the Type 1, number three and four tumors?
00:42:34.120 --> 00:42:35.410 Well, about three years ago we were thinking about the new spore and what we’re going to do,
00:42:35.152 --> 00:42:36.994 about three years ago we were meeting with limping and he said,
00:42:36.994 --> 00:42:38.349 you have a sabbatical coming up
00:42:38.349 --> 00:42:39.789 and what we’re going to do,
00:42:39.790 --> 00:42:42.112 and I was meeting with limping and he said, well,
00:42:42.120 --> 00:42:44.297 you have a sabbatical coming up
00:42:44.297 --> 00:42:46.270 when you come work in the lab.
00:42:46.270 --> 00:42:47.194 And I said, sure,
00:42:47.194 --> 00:42:48.947 the only problem is I still had
all my other administrative work, but I got an office over there and we work very closely together and I learned to laugh, even put me to work. They got me working in the lab and I’m a PhD. I did this 20 years ago, so it’s actually really good to get in the lab, but it’s about the people talking to people at coffee and understanding the different projects. I also went back to school. It went back up to Science Hill and I took immunology course. There’s Peter Cresswell, you know,
when I learned and through that, I learned what was going on in the lab even better, and I said, here’s a project we should take to the clinic. So that’s project 1, So this is a sciatica acid bound, electing its a receptor. It’s known to be on macrophages Annand. Micelles this came through a large screen that leaping had developed in the lab to find new targets. Looking at other membrane jeans home Alexa PDL one so we were going
00:43:48.347 --> 00:43:50.840 to not work on the next PDL one.
NOTE Confidence: 0.881646275520325

00:43:50.840 --> 00:43:53.080 So here sleeping myself Scotsman
NOTE Confidence: 0.881646275520325

00:43:53.080 --> 00:43:55.320 critical to this and David.
NOTE Confidence: 0.881646275520325

00:43:55.320 --> 00:43:57.402 So this is an antibody against
NOTE Confidence: 0.881646275520325

00:43:57.402 --> 00:43:58.443 us now accompany.
NOTE Confidence: 0.881646275520325

00:43:58.450 --> 00:44:00.809 Next you’re being involved and this trial
NOTE Confidence: 0.881646275520325

00:44:00.809 --> 00:44:03.914 is led by Pat Larusso and here you can
NOTE Confidence: 0.881646275520325

00:44:03.914 --> 00:44:06.460 see these are patients with lung cancer.
NOTE Confidence: 0.881646275520325

00:44:06.460 --> 00:44:08.616 On that phase one trial and there
NOTE Confidence: 0.881646275520325

00:44:08.616 --> 00:44:10.978 have been a couple of responses.
NOTE Confidence: 0.881646275520325

00:44:10.980 --> 00:44:12.228 There’s a CR here.
NOTE Confidence: 0.881646275520325

00:44:12.228 --> 00:44:15.159 There was a PR and there were a number
NOTE Confidence: 0.881646275520325

00:44:15.159 --> 00:44:18.320 of patients is the CR is appear at a
NOTE Confidence: 0.881646275520325

00:44:18.320 --> 00:44:20.714 number of patients with stable disease.
NOTE Confidence: 0.881646275520325

00:44:20.720 --> 00:44:22.460 So signs of early activity.
NOTE Confidence: 0.881646275520325

00:44:22.460 --> 00:44:23.312 That’s good.
Here is the responder I mentioned, so this drive already in phase one and we said OK, maybe we can learn more about the mechanism in the lab and more about the mechanism in the clinic and make this a trial in our long spore. So it is project one and we have other candidates of course that we’re developing as well. But this is this is a project now and again path being very closely involved the phase one results.
more science and from a biomarker. So one of the things I was able to do having been working in the lab is I put David rim together with sleeping in the company and it’s taking a few years. This is not simple stuff. You don’t just developing Immuno Chemistry Assay. You’ve gotta validate it. You’ve got to know the prevalence of that marker. Might not be so high you have to enhance for it. So David now I believe has an assay to measure S 15615 and actually it’s very interesting as he’s looked at it.
He found that when you look at patients that are high in PD, L1, the tumors tend to be low in S15. So it looks like there might be some sort of mutual exclusivity there. Which could be very important as we decide who to treat, so this works on going and the new trial we’re going to do that. Yeah, the plan is very soon to include biomarker selection. And then here’s the Travis Scott Gettinger is running as an IIT. We reached out to next cure but
00:45:41.605 --> 00:45:43.572 also through our great deal of
NOTE Confidence: 0.881646275520325
00:45:43.572 --> 00:45:44.964 work with mercantilism app.
NOTE Confidence: 0.881646275520325
00:45:44.970 --> 00:45:46.226 They’ve provided us Pember
NOTE Confidence: 0.881646275520325
00:45:46.226 --> 00:45:47.796 Lizum app for this trial.
NOTE Confidence: 0.881646275520325
00:45:47.800 --> 00:45:49.676 So now we’re going to take patients
NOTE Confidence: 0.881646275520325
00:45:49.676 --> 00:45:51.270 who have failed immunotherapy.
NOTE Confidence: 0.881646275520325
00:45:51.270 --> 00:45:52.840 And I’m hearing clinic today.
NOTE Confidence: 0.881646275520325
00:45:52.840 --> 00:45:54.100 I almost every patient.
NOTE Confidence: 0.881646275520325
00:45:54.100 --> 00:45:55.675 I see there having issues.
NOTE Confidence: 0.881646275520325
00:45:55.680 --> 00:45:56.268 You know,
NOTE Confidence: 0.881646275520325
00:45:56.268 --> 00:45:57.738 they they need what’s next
NOTE Confidence: 0.881646275520325
00:45:57.738 --> 00:45:59.140 after being in therapy.
NOTE Confidence: 0.881646275520325
00:45:59.140 --> 00:46:02.160 So for that we now need to get new biopsies
NOTE Confidence: 0.759384393692017
00:46:02.240 --> 00:46:04.655 and we’re going to have either NC
NOTE Confidence: 0.759384393692017
00:46:04.655 --> 00:46:07.027 318 that signal 15 or NC 318 plus.
NOTE Confidence: 0.759384393692017
00:46:07.030 --> 00:46:09.431 Embolism app, so we’re now going to
00:46:09.431 --> 00:46:11.150 take refractory patients and either
give them the single agent alone, hopefully someday with biomarker
or a combination with standard immunotherapy.

00:46:19.054 --> 00:46:22.388 so we’re very excited about this.
This should hopefully be open very soon.

00:46:31.860 --> 00:46:33.192 And of course, again,
I can’t emphasize enough.

00:46:38.538 So Katie Kirk came to visit,
so that was easy to form an idea.

So people who wanted to be in the picture, you know there sleeping.

There's pad.

Pleinair Charlie, I got myself a good spot.

You can see we have a team.

It's all these people.

The other ones were doing the work

The team we have probably have.

I know we have the best phase

when you did in the world.

So I’ve talked.

I’ve gone through a couple of

little vignettes you can see.
I’m excited, I’m enthusiastic. 
I think we’ve made a difference. 
I’ve seen it myself. 
There’s nothing like seeing a patient who’s alive 10 years later that you’ve treated it with your own clinic. 
What is the future? 
But it’s very hard to predict the future. 
But can we cure metastatic lung cancer with immunotherapy? 
And I’ve been asking this question to a lot of people and I’m going to say yes. 
But in some cases, 
or at least patients can remain alive with controlled disease, we’ve seen it.
I started to Scott earlier today in the clinic we have 10 years survivors from the very first trial. Maybe 1020 of them. Know we have people who are alive. Maybe that 10 years, but ten years up to 10 years at seven six years we used to celebrate survival at MD Anderson in stage three disease at five years. So it might be time to start getting these patients together. We have to learn though a little bit more. My point now to all of you. Is we can treat these patients. It was well tolerated,
but we need to know in advance who
are these patients so that those who
can get immunotherapy alone can get it.
And those that the combinations
of drugs or chemotherapy.
They can get it. So that’s where I think we need to
put all of our efforts in the next few years.
So do we need to personalize immunotherapy?
Absolutely. We spent 20 years
personalizing targeted therapy.
It’s still a small population that
we’re treating. We need biomarkers.
We need better combos.

We need more science.

We need innovative trial designs, collaboration, and public private partnerships.

I would say to all of you watching right now. The future is now I’m going to give you an opportunity to work with us in the last slide. So what are we waiting for? It’s time to target immunotherapy, and you know, we can’t just give these drugs to all patients. We’ve we’ve we’ve, it’s amazing the number of diseases that it benefited.
All diseases benefit to some extent, but there are cold tumors there too, is it don’t have much PDL? One we have to better understand this and that’s going to mean better science in the clinic. Now Scott shared this with me this morning and this is our exceptional responder cohort, so you can see these are patients for whom we have tissue, and you can see months from starting immunotherapy. So we’ve got quite a few there that are out three four years. So now what we need to do is we
00:49:30.838 --> 00:49:32.522 need complete analysis of these
NOTE Confidence: 0.903504848480225
00:49:32.522 --> 00:49:34.312 patients apples to inform future
NOTE Confidence: 0.903504848480225
00:49:34.312 --> 00:49:36.279 studies to personalize immunotherapy.
NOTE Confidence: 0.903504848480225
00:49:36.280 --> 00:49:37.165 That’s on going.
NOTE Confidence: 0.903504848480225
00:49:37.165 --> 00:49:39.230 My prediction is it’s not going to
NOTE Confidence: 0.903504848480225
00:49:39.297 --> 00:49:41.265 just sequencing if we do sequence,
NOTE Confidence: 0.903504848480225
00:49:41.270 --> 00:49:42.570 we’re going to sequence.
NOTE Confidence: 0.903504848480225
00:49:42.570 --> 00:49:44.195 So tumor and the host.
NOTE Confidence: 0.903504848480225
00:49:44.200 --> 00:49:45.970 So maybe this generations project will
NOTE Confidence: 0.903504848480225
00:49:45.970 --> 00:49:48.200 help us that’s being done at Young Haven,
NOTE Confidence: 0.903504848480225
00:49:48.200 --> 00:49:50.209 but this is something we can do.
NOTE Confidence: 0.903504848480225
00:49:50.210 --> 00:49:53.276 We will do, we must do.
NOTE Confidence: 0.903504848480225
00:49:53.280 --> 00:49:54.572 Adaptive trial designs and
NOTE Confidence: 0.903504848480225
00:49:54.572 --> 00:49:55.864 new protocols are needed.
NOTE Confidence: 0.903504848480225
00:49:55.870 --> 00:49:57.814 I didn’t have much time to
NOTE Confidence: 0.903504848480225
00:49:57.814 --> 00:49:59.110 talk about this today,

but a lot of this tissue sampling has come from the battle trial.

It’s 15 years since we started that trial at MD Anderson.

I think the same principles would apply adaptive trial design.

Europe, England has a national lung matrix project.

I think this is something that we certainly want to think about.

Targeted therapy for patients based on biomarkers we already happened in the US.

This is the lung map trial in which I’m the Pi.

A large public private partnership.
About 100 of us in the leadership working together, we have this open at yellow or one of the number one cruisers. Her child does a great job with this, and if so, how? At the VA, targeting patients with mutations but also patients who are immune resistant. There are many new drugs we need to work with these drugs. We need to combine these drugs. Again, this I just meant to show that if we combine them, You have to do it rationally and
we have to do it based on the science and what we’ve learned about the immune microenvironment. 

This is an amazing trial that Scott leads with Richard for Val, David, Hafler, Kurt, Katie. 

We have ample amount of all map now and approved regimen and we have about 3040 patients in this trial. 

Everyone gets tissue, blood and stool for microbiome and we’re putting the markers together. 

It’s just at the point now. 

It’s been 3 four years,
then we're going to try to get some information on who benefits and who doesn't. So finally I told you I'd give you a challenge. I would propose that we need to do the eye bulldog trial, and I've been talking to Pat and best phase one and drug developer. I know and she'll get the drugs. She understands a science Ed Captain. We need him. It’s just the amazing, most amazing person at bringing teams together and where we work so well together. So we’re going to actually take a trial. Now we're going to try to use biomarker development biomarker prediction to
treat patients based on that with trials and the reason I want to show this now. Is we’re now accepting applications, so I’m announcing a new PO1 group that’s forming today. We’re going to start having some meetings. I’d like to take the best science of yell, the best clinical science. I’d like to merge them together. I can tell you it’s not really easy. In fact, most people tell you it can’t be done. Used to work a lot of the Folkman he used to tell me that’s exactly the time when you should do it,
00:52:18.440 --> 00:52:19.934 so we're going to make this
NOTE Confidence: 0.815827786922455
00:52:19.934 --> 00:52:21.410 happen and I'm very excited,
NOTE Confidence: 0.815827786922455
00:52:21.410 --> 00:52:23.498 and I think I’ve shown you
NOTE Confidence: 0.815827786922455
00:52:23.498 --> 00:52:25.340 that progress can be made.
NOTE Confidence: 0.815827786922455
00:52:25.340 --> 00:52:28.260 So I just want to thank all of you today.
NOTE Confidence: 0.815827786922455
00:52:28.260 --> 00:52:30.297 It’s just been an amazing team effort.
NOTE Confidence: 0.815827786922455
00:52:30.300 --> 00:52:32.636 I want to especially thank the Yale School
NOTE Confidence: 0.815827786922455
00:52:32.636 --> 00:52:34.679 of Medicine by Albert for his support.
NOTE Confidence: 0.815827786922455
00:52:34.680 --> 00:52:36.654 The teacher grants that have led to
NOTE Confidence: 0.815827786922455
00:52:36.654 --> 00:52:39.025 these spores and now Nancy Brown and her
NOTE Confidence: 0.815827786922455
00:52:39.025 --> 00:52:40.820 team have continued to support this.
NOTE Confidence: 0.815827786922455
00:52:40.820 --> 00:52:43.004 Brian Smith and of course Charlie in
NOTE Confidence: 0.815827786922455
00:52:43.004 --> 00:52:45.027 the Yellow Cancer Center for all the
NOTE Confidence: 0.815827786922455
00:52:45.027 --> 00:52:47.503 money we get from the NCI we get all
NOTE Confidence: 0.815827786922455
00:52:47.503 --> 00:52:49.279 the resources of the Cancer Center.
NOTE Confidence: 0.815827786922455
00:52:49.280 --> 00:52:51.072 We get additional money for the DRP&C
programs that career development and that’s really important. So with that out. Thank you. And hopefully we have time for a couple of questions. Thank you very much. Or thank you. That was just fabulous. And congratulations to you and really everyone on the team or just amazingly impactful work in this field. I got some of the team here so I had a little bit of a live audience so. Excellent so folks should submit their
questions on the chat function,

but I’ll start while people are typing

so you have a couple of questions.

One that I’m just curious ‘cause I’ve I’ve

but I didn’t fully appreciate

when you look at mutation type

There seemed to be potentially a

difference depending on the mutation

type where it almost look like.

They’re confidence limits were

not overlapping.

did I misinterpret that

no well, the good news is that both

mutation types benefited in this
00:53:55.946 --> 00:53:58.066 trout in the metastatic setting.

00:53:58.070 --> 00:54:00.387 There is much more of a benefit

00:54:00.387 --> 00:54:02.753 for the exon 19 deletion versus

00:54:02.753 --> 00:54:04.913 the exon 21 point Mutation.

00:54:04.920 --> 00:54:06.392 As you can imagine,

00:54:06.392 --> 00:54:08.600 you would think that deletion might

00:54:08.674 --> 00:54:11.020 be less likely to become resistant.

00:54:11.020 --> 00:54:13.306 But yeah, I think you know

00:54:13.306 --> 00:54:14.830 the numbers there are.

00:54:14.830 --> 00:54:15.895 About equivalent there,

00:54:15.895 --> 00:54:18.920 one of them does a little bit better,

00:54:18.920 --> 00:54:21.524 but I think the good news there

00:54:21.524 --> 00:54:24.140 was that both, or at least quite

00:54:24.140 --> 00:54:25.640 well significant compared to.

00:54:25.640 --> 00:54:27.146 The one the travel, of course,
was empowered to compare the two.

And then sort of on a related note.

Curious to see what your you know what your expectations are for IO in the future value in the Agement.

That’s a great question, so I of course trials are ongoing so.

They are being done in many cases.

without biomarker, so I worry a little.

I didn’t mention it, I know I assume
most of us are familiar with this, but the idea is that you can get with these immune therapies while mostly low level. Certainly pneumonitis is something to worry about, and Carditis and other things. In the aggregate setting, I think that I would give it a 5050. Whether these trials will be positive. It’s hard to file. We don’t know the PD L1 status often of these. These tumors were not following micrometastatic disease. I think in the future shortly we’re
00:55:36.038 --> 00:55:38.175 going to use MRD techniques and these
NOTE Confidence: 0.791537046432495
00:55:38.175 --> 00:55:40.460 bespoke models to know who has minimal
NOTE Confidence: 0.791537046432495
00:55:40.460 --> 00:55:42.854 residual disease and much rather see it.
NOTE Confidence: 0.791537046432495
00:55:42.860 --> 00:55:45.303 Try where we know that someone has
NOTE Confidence: 0.791537046432495
00:55:45.303 --> 00:55:47.052 minimal residual disease and then
NOTE Confidence: 0.791537046432495
00:55:47.052 --> 00:55:48.966 use that route immune therapy to
NOTE Confidence: 0.791537046432495
00:55:48.966 --> 00:55:50.689 enhance that so it’s being done
NOTE Confidence: 0.791537046432495
00:55:50.689 --> 00:55:52.866 sort of just as the next step and
NOTE Confidence: 0.791537046432495
00:55:52.866 --> 00:55:55.127 it might be that these are tumors
NOTE Confidence: 0.791537046432495
00:55:55.127 --> 00:55:57.560 that are not driven by PDL 1 maybe.
NOTE Confidence: 0.791537046432495
00:55:57.560 --> 00:56:00.420 They are the type 1 three or five or four.
NOTE Confidence: 0.791537046432495
00:56:00.420 --> 00:56:02.976 So I do worry about that a little bit,
NOTE Confidence: 0.791537046432495
00:56:02.980 --> 00:56:04.678 but you know, like anything else,
NOTE Confidence: 0.791537046432495
00:56:04.680 --> 00:56:06.378 depending on the population, they get.
NOTE Confidence: 0.791537046432495
00:56:06.380 --> 00:56:07.928 If it’s a highly smoking related
NOTE Confidence: 0.791537046432495
00:56:07.928 --> 00:56:09.343 population that might have higher
tumor mutational burden, perhaps it will be positive, but no, it gets all the same questions. How long to treat know what are you treating? But I’m glad that the experiments are ongoing and hopefully there are blood samples that are being obtained from those trials so that we can look and see what’s happening in real time now. The other question you answer is. But I’d love to do, you know, we know that targeted therapy you have in each year for mutation, have in each year for mutation, 80% chance of tumor, will respond to patient.
Feels better within days, so why not use immunotherapy targeted therapy early on, knowing that resistance will ultimately develop and then bring on the immune therapy, which takes awhile to work, but will have a mug shot but will have a much more durable response that’s been tried an at least in lung cancer. The toxicity has just been. Unbearable both in Asia and in the US. Not sure why, but I guess the reactivation of the immunity in patients that are getting these EGFR agents that do tend to have issues with the skin and the
long term institutional lung disease. Those toxicities have precluded that so far. That said, there are other ways to other agents that can be looked at that are now being tried. Lag 3 Tim. all should be looked at. So I think that. That has to be the next step, because each year for mutated disease, as good as it is, at least in the metastatic setting, we still have many patients. In fact, most will recur,
and so I think trials are warranted there and then.

You know, I’m hoping that in the Dora the longer duration of therapy with better agent in an earlier setting will result in.

Curious, but we don’t know that yet either.

Going to follow those patients for awhile for survival.

Thank you. Actually a few questions coming in one comment that will offer quickly is Stephanie Lien Rights.

Congrats, beautiful multiple exclamation points Stephanie.

Thank Stephanie Pat Larusso asks, do you think the scenario will be the same with G12C rash mutations
00:58:13.752 --> 00:58:16.890 in combination with IO? OK so

NOTE Confidence: 0.791898965835571

00:58:16.890 --> 00:58:20.215 so I didn’t mention that but that’s

NOTE Confidence: 0.791898965835571

00:58:20.215 --> 00:58:23.134 K wrasses, been the Holy Grail.

NOTE Confidence: 0.791898965835571

00:58:23.134 --> 00:58:26.080 So G12C mutations in lung cancer

NOTE Confidence: 0.791898965835571

00:58:26.175 --> 00:58:28.767 account for about 12 to 13%.

NOTE Confidence: 0.791898965835571

00:58:28.770 --> 00:58:32.676 That’s more than each year for mutations.

NOTE Confidence: 0.791898965835571

00:58:32.680 --> 00:58:35.456 Now there will be a big talk actually.

NOTE Confidence: 0.791898965835571

00:58:35.460 --> 00:58:37.896 12 C&K Ras the engine drag asmo.

NOTE Confidence: 0.791898965835571

00:58:37.900 --> 00:58:39.988 I believe this Sunday or Monday.

NOTE Confidence: 0.791898965835571

00:58:39.990 --> 00:58:41.730 We know that their responses.

NOTE Confidence: 0.791898965835571

00:58:41.730 --> 00:58:43.818 You know that’s been presented already.

NOTE Confidence: 0.791898965835571

00:58:43.820 --> 00:58:46.172 In fact, Yosi and I wrote an

NOTE Confidence: 0.791898965835571

00:58:46.172 --> 00:58:47.990 editorial on this last year.

NOTE Confidence: 0.791898965835571

00:58:47.990 --> 00:58:49.868 We also know that the activity

NOTE Confidence: 0.791898965835571

00:58:49.868 --> 00:58:51.973 was best in preclinical models in

NOTE Confidence: 0.791898965835571

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immune competent animal models. So I do think that those agents are just begging to be combined with a new therapy. The one thing we don’t know yet and hopefully will see this weekend. Is what is the durability of response for K Ras agents alone you worry since K races so upstream, but they’re going to be so many bypassed pathways there. Will it have a median duration of response of at least six months or more? In fact, if not, I probably have to be combined so my phone is that very nice that we have these agents.
the Q 12 see not as good in colon cancer, of course, but that’s a smoking related KRS abnormality. Now we do have data that K Rasputin patients to respond to immunotherapy. But I think that combination is something that hopefully we’re already doing here. So Sarah Goldberg already is running trials. Navid have fares as a trial in the face. One group. These are all things we’re studying here. Final question from David.
Rim is a diagnostic test needed to see who will benefit in the admin setting or should every mutation patient get? I guess those emergent OSI here, right? And at this point, no. I think everyone who's EGFR Mutant. You know, you know. Again, you know there are going to be some who say we don’t have survival data. I can share if I were giving this talk a week from now. I think I could put the nail in the case because you know, certainly if when we’re not metastasized to the brain.
I think that’s a good thing, but I think that yes, you know we’re going to have to learn from this. I can’t wait till dawn when gets those samples and he can sequence them and tell us who’s going to metastasized to the brain. We can look at the cell free DNA and know that someone is developing early resistance and maybe we get Katie. Some tumor actually can develop an animal model. There’s still room to do better,
but I think right now, assuming approval, I think will use this. Then one of our surgeons right here. I have to convert him that he should send the sample for each year from Mutation and hopefully will do that. And hopefully David will help me with that. Alright, thank you, I know we’re out of time is a fantastic talk. Great, great work. Thank you for all that you’re doing in your leadership. And again, thank you for a fantastic presentation. Thanks for all your support. Again. It’s it’s the Cancer Center that supports
the teams that really can make the difference that can help the patients.

Eventually everyone have a good day and will see you next week.