00:00:07.940 --> 00:00:12.567 everybody. Welcome to our session on behalf
00:00:12.567 --> 00:00:17.117 of Yale University and Yale Cancer Center.
00:00:17.120 --> 00:00:20.136 I'm pleased to have you with us as
00:00:20.136 --> 00:00:23.679 part of the Yale Engage Cancer series.
00:00:23.680 --> 00:00:26.450 This session is entitled defining.
00:00:26.450 --> 00:00:28.575 Mechanisms and biomarkers of sensitivity
00:00:28.575 --> 00:00:31.430 and resistance to anti cancer treatments.
00:00:31.430 --> 00:00:37.258 I'm a medical oncologist and have a interest
00:00:37.258 --> 00:00:40.390 in drug development and head neck cancer.
00:00:40.390 --> 00:00:44.046 And we have a phenomenal panel of Yale
00:00:44.046 --> 00:00:46.669 faculty members and Anna corporate
00:00:46.669 --> 00:00:49.369 guest Susan Galbraith from Etsy.
And hope to have a very very interactive session. I’d like to start with a few housekeeping items. The program format as I said, is going to be each of our panel members giving a brief about 5 minute introduction to the work that they do. What they see is as key questions. We know that to attack cancer we need team science. We need collaborations within our.
organization and across different sectors. Academic, public and industry and Yale engage was designed to build these connections, particularly between Yale scientists and industry leaders. To keep the discussion lively, we welcome questions. Some have been submitted ahead of time and you’ll have the ability to submit them through the Q&A function. On the Web and R we have an enormous amount of expertise among our panelists and will be. Monitoring those questions as they come up and try to get to as
many of them as possible and I I
want you to know that this web,
nor is being recorded,
so now I’m really pleased to be
able to introduce Charlie Fuchs.
He’s the secular professor of
medicine and medical oncology and
a professor of chronic disease
Epidemiology here at Yale.
He’s the director of the Yale
Cancer Center and Position in chief
at Smilow Cancer Hospital.
Charlie.
Forever thank you and thank you for
your leadership on this and welcome
to all the attendees to what is now our third Yale Engage cancer event and it’s really been an exciting and incredibly productive series of forms. So please it could join us for this third one. You know, we we all recognize that despite the fact that we’re dealing with a global pandemic, the consistent impact of cancer on public health. And the morbidity and mortality and costs on our population. Or considerable and it remains one of the great challenges in medicine. And it also is one of the
NOTE Confidence: 0.871820628643036
00:03:12.409 --> 00:03:13.283 largest investments.
NOTE Confidence: 0.871820628643036
00:03:13.290 --> 00:03:16.216 I think that goes on and healthcare
NOTE Confidence: 0.871820628643036
00:03:16.216 --> 00:03:18.321 research and drug development and
NOTE Confidence: 0.871820628643036
00:03:18.321 --> 00:03:21.023 our our our efforts at Yale is
NOTE Confidence: 0.871820628643036
00:03:21.023 --> 00:03:23.777 to really tackle this challenge.
NOTE Confidence: 0.871820628643036
00:03:23.780 --> 00:03:26.629 Yeah Liz had a long legacy in
NOTE Confidence: 0.871820628643036
00:03:26.629 --> 00:03:29.019 Cancer Research and cell biology,
NOTE Confidence: 0.871820628643036
00:03:29.020 --> 00:03:29.896 genetics, pharmacology,
NOTE Confidence: 0.871820628643036
00:03:29.896 --> 00:03:31.648 immunology, among other elements.
NOTE Confidence: 0.871820628643036
00:03:31.650 --> 00:03:35.880 And I think a lot of the history of success,
NOTE Confidence: 0.871820628643036
00:03:35.880 --> 00:03:37.664 including four Yutema therapies,
NOTE Confidence: 0.871820628643036
00:03:37.664 --> 00:03:40.340 come out of this University were
NOTE Confidence: 0.871820628643036
00:03:40.414 --> 00:03:42.717 privileged to work at one of the
NOTE Confidence: 0.871820628643036
00:03:42.717 --> 00:03:44.851 national one of the original
NOTE Confidence: 0.871820628643036
00:03:44.851 --> 00:03:46.456 National Cancer Institute,
designated Cancer centers, and has been a really an area that research that is as built a legacy of great innovation as well. Smilow cancer hospital. Our clinical center. Is celebrating its 10th anniversary and is a robust operation that now sees about 48% of every newly diagnosed cancer patient in the state of Connecticut. And really, we view that through the science and through this robust clinical operation we really are committed to moving, discovery scientific discovery into the clinic.
Really pleased with the team that's been assembled today, our first and Yale engage cancer was focused on immunobiology, our second. Was focused on novel therapeutics, and the third really ties it all together, which is to understand now, given these efforts to develop new drugs, new targets, how do we understand resistance? How do we understand sensitivity? And how do we further enhance our approaches to cancer therapy? Integral to this fight is our collaboration with industry,
and we’re so pleased to have Doctor Susan Galbraith join us as our industry partner on the panel, and we realize that. So many of you in the audience come from the biotech and pharma. An really part of this effort. Beyond hearing from these experts in their insights is to really begin a conversation. Because one thing we really welcome here at Yale is to collaborate with you. We want to build strategic partnerships with all of you. Because ultimately this fight against cancer. Yes,
it requires each of these domains on the slide, but it requires a community focused on every aspect, and that includes academia and industry in biotech. So one thing I want to invite you today is to ask questions, but after this form, please reach out to us. And let’s think about ways we can work together. I think we have a lot of resources we can bring here at Yale to...
partner with all the great things you’re all doing and we look forward. To continuing this conversation long after this form, so again, thank you for joining and I’ll turn it back to Barbara. Thank you Charlie. I think that’s a great introduction to what we’re trying to do here I just had a brief opportunity to scroll through the list of 100 participants an it’s a formidable group, including GAIL scientists, industry partners. Alumni are supporters, so I think that we can anticipate some some pretty hard hitting
00:06:28.272 --> 00:06:30.978 questions from that group. So we've.

00:06:30.978 --> 00:06:34.490 We've tried to arrange these talks so that.

00:06:34.490 --> 00:06:36.314 We hope that there's a little

00:06:36.314 --> 00:06:38.131 bit of a natural progression

00:06:38.131 --> 00:06:40.247 in the scientific questions,

00:06:40.250 --> 00:06:42.693 and Dan the approaches that are are

00:06:42.693 --> 00:06:44.470 taken to understanding resistance.

00:06:44.470 --> 00:06:45.577 As I said,

00:06:45.577 --> 00:06:47.791 every speakers been asked to sort

00:06:47.791 --> 00:06:50.997 of reflect a little bit on what’s her,

00:06:51.000 --> 00:06:52.215 his core expertise.

00:06:52.215 --> 00:06:53.835 What questions drive the

00:06:53.835 --> 00:06:55.989 research and how they hope to,

00:06:55.990 --> 00:06:59.758 or Yale hopes to work with industry partners.

00:06:59.760 --> 00:07:03.212 To address cancer cancer

00:07:03.212 --> 00:07:05.298
00:07:03.212 --> 00:07:04.938 treatment resistance.
NOTE Confidence: 0.85655349890391
00:07:04.940 --> 00:07:06.974 And what kinds of capabilities and
NOTE Confidence: 0.85655349890391
00:07:06.974 --> 00:07:09.388 resources need to be brought to bear?
NOTE Confidence: 0.85655349890391
00:07:09.390 --> 00:07:11.679 So each of those speakers has been
NOTE Confidence: 0.85655349890391
00:07:11.679 --> 00:07:14.519 asked to go only for about 5 minutes?
NOTE Confidence: 0.85655349890391
00:07:14.520 --> 00:07:16.970 I've been told that I should be
NOTE Confidence: 0.85655349890391
00:07:16.970 --> 00:07:18.968 ruthless and and cut you off.
NOTE Confidence: 0.85655349890391
00:07:18.970 --> 00:07:21.539 If you go over and and that
NOTE Confidence: 0.85655349890391
00:07:21.539 --> 00:07:23.289 will be hard to do.
NOTE Confidence: 0.85655349890391
00:07:23.290 --> 00:07:25.090 'cause I know the talks
NOTE Confidence: 0.85655349890391
00:07:25.090 --> 00:07:26.890 are going to be great,
NOTE Confidence: 0.85655349890391
00:07:26.890 --> 00:07:29.050 but let me start by introducing
NOTE Confidence: 0.85655349890391
00:07:29.050 --> 00:07:30.130 Doctor Katie Palitti.
NOTE Confidence: 0.85655349890391
00:07:30.130 --> 00:07:32.290 She's an associate professor of pathology
NOTE Confidence: 0.85655349890391
00:07:32.290 --> 00:07:34.809 and Medicine leader in our Cancer Center.
NOTE Confidence: 0.85655349890391
00:07:34.810 --> 00:07:36.250 Through those answering signaling
cancer signaling networks program, as well as a leader of our lung spore program and Katie. Think it away. Thank you very much, Barbara. And I’m really delighted to have the opportunity to speak here today and tell you about some of the things that we’re interested in. I have a cancer biology lab here really with a focus on lung cancer and one of the areas that we are really interested in studying is working on resistance and resistance to various cancer therapies including targeted.
Some of the things that we think about a lot and work on. I'm really interested in understanding the relationship between tumor genotype and drug sensitivity. We study the influence of the tumor micro environment on sensitivity to different therapies and also investigate mechanisms of drug tolerance. So why do some cells die when you apply a therapy and instead other cells do not die and stick around and serve as the fertile ground for the emergence of drug resistance?
And then we also investigate new approaches based on the science that we discover to overcome and or to prevent the emergence of drug resistance. We use specimens and data from patients, so we have a very robust biopsy program. Within the context of the Lung Cancer Group, where we can obtain biopsies from patients.
their treatment with therapies,

and we can generate patient derived

but also then analyze the

data and information to really

understand resistance in patients.

We use these models to generate

or these specimens to generate

patient drive Zeno graphs as well,

and also 2D or 3D cultures

from patient specimens,

and we also extensively work

with genetically engineered mouse

models of lung cancer that we can.

I used to study resistance and in

that regard I’d like to tell you today
about some work that we have been doing in the field of EGF receptor, mutant lung cancer. Next slide, please.

To really use models to study resistance to the EGFR tyrosine kinase inhibitor, also Merton.

If and this is a work that really illustrates a partnership between Academia and investigators in academia and work that we’ve done together with Astra Zeneca and also working with Garden Technology and work that was published recently this year and so EGF receptor mutations are found in about 15% of lung cancers and can
be targeted with tyrosine kinase inhibitors and one of the most recent ones.

Is this tyrosine kinase inhibitor awesome Merton Eben?

So we can take our genetically engineered mouse models and ask the question what happens?

If you have mouse models of EGF receptor, mutant lung cancer, and you treat them with awesome Merton, if and so we took my sweet, treated them till the emergence of resistance.

And when we looked at resistant tumors to see what was happening, we found that almost 50% of the tumors
that emerged had secondary mutations in EGF receptor that confer resistance to awesome American if and so.

With that information we can actually then go ahead using these models.

So we’ve discovered new mechanisms.

We can now use these models for preclinical testing and test new therapies.

We can also with this information go into human specimens and data and analyze the relevance of the resistance mechanisms there, and so.

For example, in this study we found that the mutations that were emerging were particularly relevant to the L.
00:11:49.040 --> 00:11:51.960 so at our subset of EGFR mutant tumors,
NOTE Confidence: 0.838195204734802
00:11:51.960 --> 00:11:54.144 so there was an allele specificity
NOTE Confidence: 0.838195204734802
00:11:54.144 --> 00:11:56.397 that was revealed through our studies
NOTE Confidence: 0.838195204734802
00:11:56.397 --> 00:11:58.581 in mouse models and then working
NOTE Confidence: 0.838195204734802
00:11:58.581 --> 00:12:00.349 with colleagues like Mark Lemon.
NOTE Confidence: 0.838195204734802
00:12:00.350 --> 00:12:03.010 Here, you’re going to hear from next.
NOTE Confidence: 0.838195204734802
00:12:03.010 --> 00:12:06.195 We can really then study the biochemical
NOTE Confidence: 0.838195204734802
00:12:06.195 --> 00:12:08.909 properties in detail of these mutants.
NOTE Confidence: 0.838195204734802
00:12:08.910 --> 00:12:11.328 Next slide, please.
NOTE Confidence: 0.838195204734802
00:12:11.330 --> 00:12:13.636 So we also are working extensively
NOTE Confidence: 0.838195204734802
00:12:13.636 --> 00:12:16.338 to take these models that we have
NOTE Confidence: 0.838195204734802
00:12:16.338 --> 00:12:19.067 and sort of take them to the next
NOTE Confidence: 0.838195204734802
00:12:19.067 --> 00:12:21.779 level to study some of the more
NOTE Confidence: 0.838195204734802
00:12:21.779 --> 00:12:23.615 complex mechanisms of resistance,
NOTE Confidence: 0.838195204734802
00:12:23.620 --> 00:12:26.308 and we have modified for example this
NOTE Confidence: 0.838195204734802
00:12:26.308 --> 00:12:28.608 initial mouse model of EGF receptor,
mutant lung cancer to incorporate additional genetic alterations that are also found in humans in EGFR mutant lung cancer, including, for example, tumor suppressor gene alterations using in vivo CRISPR CAS 9 gene editing and so now. We can study how those additional alterations are impacting tumor progression, sensitivity to therapies, and the phenotypes of tumors. As I mentioned in my first slide, we also have a robust program to generate patient derived models, and here is really an illustration.
of sort of the different.

PDX is that we’ve generated across various different oncogenic subgroups of lung cancer with different oncogenic driver alterations, and so we’re using these models. To really study resistance in human specimens and really use them to study heterogeneity of human tumors, signaling network alterations, and the molecular profiles that you can have in these human who tumors can have in these human who tumors with or without drug treatment. Thank you.
00:13:38.892 --> 00:13:42.796 much there for the other speakers to riff
00:13:42.796 --> 00:13:47.136 off of and and to set up our questions.
00:13:47.140 --> 00:13:49.678 Next, let me introduce Mark Lemon,
00:13:49.680 --> 00:13:51.424 distinguished Professor of pharmacology.
00:13:51.424 --> 00:13:54.899 You see his leadership roles in the Cancer
00:13:54.899 --> 00:14:00.874 Center in Cancer Biology Institute.
00:14:00.880 --> 00:14:03.757 You know a wealth of expertise in
00:14:03.757 --> 00:14:06.367 biology and structural biology to the
00:14:06.367 --> 00:14:08.532 very interface with drug development
00:14:08.532 --> 00:14:11.676 and and disease based research and so.
00:14:11.680 --> 00:14:14.270 Looking forward to your comments, mark.
00:14:14:080 --> 00:14:16.212 Thank you very much,
00:14:16.612 --> 00:14:18.144 Robert and good afternoon.
00:14:18.150 --> 00:14:20.838 So a great pleasure to be here.
I look forward very much to hearing discussion later on. As Barbara mentioned, I'm really a basic scientist interested in how molecules work. My core expertise really is in biochemistry and structural biology. The focus of most of our work is detailed understanding of how molecules and networks involved in oncogenic signaling actually do work and do not anatomic detail. Where we can and quantitatively understand how their properties are changed by oncogenic and resistance mutations.
As Katy mentioned, work we’re doing with her and how we can then use that information to guide mechanistically driven personalized medicine or put the biochemistry into personalized medicine. Those kinds of thoughts. So our main focus in general is the class of receptors that Katie discussed. The growth factor receptors that have interested Harrison Chinese have interested Harrison Chinese domains like EGF receptor. As you know, and as key to describe, these are key targets for cancer therapy, particularly lung cancer.
and is clear in general in advancing approaches to controlling their behavior.

So the behavior with drugs dealing with resistance really requires us to understand the molecular mechanisms and understanding well enough that we can manipulate them in a predictable way and also manipulate their complex so the networks.

Recently, and the first relates to what Katie has been discussing at the level of growth, acquired resistance and primary resistance,
and we've actually been working with Katie quite a bit to understand details of how secondary mutations in EGFR cause resistance. As she mentioned, with the automotive resistance mutations and the additional key colon network is to use that understanding as it develops to decide when to use which inhibitor and how to come up with new and indeed repurposed inhibitors in resistance situations. Not going back to two other working in the lab, one of our recent first time
has been to identify and target
driver mutations in neuroblastoma, which is one of the most common pediatric cancers.
And this is related work we’ve been collaborating with the Children Psychology Group on another receptor tyrosine kinase, a bit like EGFR, and sequencing out consumers from 1600 patients. That gave us a list with mutations that we analyzed biochemically. Real transformation did a full work up on them and show from that out.
About 14% of neuroblastoma without dependent, and we developed a computational model that you can see in the middle of the left-hand part of the slide. We can predict which mutations are actionable. Working on that and refining to identify out dependent tumors in the clinic and what but importantly this quickly let us understand that some variants are resistant to 1st generation out computers result and it does not work in Europe. Last over and we also learned that the
stable of 1st generation are contributors.

We're not that different from one another and impedes.
In particular, we have one.
We have to be careful to which drug you choose for the trials, because there's a limited number of patients in pediatric, so more monster pick the right one and over all those considerations, using their biochemistry channel distal mat in it, which is now looking promising in neuroblastoma, although of course we are now experiencing
00:17:39.996 --> 00:17:41.500 resistance that we’re working on,
00:17:41.500 --> 00:17:43.318 and I just want to illustrate that as a
00:17:43.318 --> 00:17:45.262 key approach combining biochemistry and
00:17:45.262 --> 00:17:47.377 structural biology and computational aspects.
00:17:47.380 --> 00:17:49.424 But we could use in principle for
00:17:49.424 --> 00:17:50.979 any receptor types in Chinese.
00:17:50.980 --> 00:17:54.068 So next slide please.
00:17:54.070 --> 00:17:56.219 We also very interested in a new
00:17:56.219 --> 00:17:58.162 aspect of getting away from inhibiting
00:17:58.162 --> 00:18:00.931 receptors per say as we tend to do
00:18:00.931 --> 00:18:02.799 instead correcting their signaling.
00:18:02.800 --> 00:18:04.672 So we’re all familiar with biased
00:18:04.672 --> 00:18:06.979 agonists for G protein coupled receptors,
00:18:06.980 --> 00:18:09.140 which can promote different responses to
00:18:09.140 --> 00:18:11.867 the same receptors as strength on the left.
The color of signaling, whether it’s orange, yellow, green or blue.

Many common drugs that we take, her bias GPS are agonists, and there’s actually a lot of effort for example to develop biased agonists of opiate receptors retaining analgesic effects. But without the associated problem problems of the opiates, we don’t do that for receptor tyrosine kinases.

In the light there traditionally thought of as being binary signaling systems, either on or off as an illustrated here, but we recently showed in the
a couple of years ago would continue to work on that. Prices have color in their signaling two and as illustrated on the right, the same receptor EGF receptor. Again in this case can give you can promote self liberation or differentiation depending in the same cell depending on which growth factor is used to activate it, and this reflects you know a different dimer structure, asymmetric or symmetric, for the two ligands with altered dimerization and signaling.
kinetics that define specificity,

it turns out the mutations in glioblastoma shift signaling to the right,

making it more proliferative.

That’s one of their.

At key issues,

even with small structural changes,

now that we understand the structural basis for this but through crystallography and so forth,

we believe that it’s possible to develop biologics that will do the opposite.

Imagine,

for example,

an antibody that could shift EGF activated in cancer we mutation
allele with living shift signaling to the left making it differentiative.
This could be a really powerful approach to signaling, switching or correcting signaling from preparations. Differentiation is actually 1 proof of principle in that with kit and stem cell factor that causes that was been working on. At Stanford, so next slide please. And so finally. We’ve also been focusing on an undruggable target the pseudo kinases. About 10% of the kinases in kind
of is inactive and the blue ones

Many of them don’t even buy native P,

PK7 involved in wind signaling

and involved in several councils,

but have been totally

ignored as drug targets.

One hypothesis is that they simply

by switching confirmations to bind

downstream signaling molecules.

We recently determined in this.

Paper in 2022,

generated here a bunch of
structures and script screen for small molecule inhibitors to see if we could bring in principle drug these in the middle here in the structure you can see a drug. It’s actually pronounced enable inhibitor bound to one of these pseudo kinases that doesn’t even bind 80P and M as shown in the top right. We’ve demonstrated using hydrogen determine change studies that put out maybe induces conformational changes in role one as it binds and so the idea is that this might inhibit signaling interactions that
naturally there’s a lot enormous amount

And so forth.

But early studies of signaling effect suggests that banana can inhibit

went dependent rule one signaling,

and so the idea of sharing centrally

disruptors like this could be

valuable tools for understanding.

See Tiffany signaling,

but also targeting them where they play

known roles in cancer and other diseases,

and so far they’re all being

hit the articaine ones.

For example, with antibodies.
So that’s about my brief summary. That’s all I wanted to say, so thank you very much for attention, and I look forward to your questions. Thank you very much Mark for that wonderful discussion.

Next, I’ll be introducing Meghan King, associate professor of cell biology and molecular, cellular and developmental biology. Program leader in our Cancer Center and I think notable partly for having been elected by the her fellow faculty here at Yale School of Medicine.
As past president of our faculty Senate equivalent, the Faculty Advisory Council where she also showed exceptional leadership.

Sort of in that other realm, and she’s going to be talking to us about very impactful work regarding resistance to PARP inhibition.

Alright, so thank you. I’m also a basic scientist and over the past decade. It’s really been my interactions with my colleagues here in the Yale Cancer Center that is driven my group with expertise in genome integrity to really
focus on those aspects that have impacts for cancer therapies.

So I’m going to start with this classic example of synthetic lethality, and that are is specifically PARP inhibitors in the context of Bracco Wanan bracket, two mutations, although of course these therapies have incredible promise. It’s well established now that the acquired resistance is a major bottleneck for the durability and efficacy of these treatments, and so, how do we tackle this problem and other opportunities that are presented when...
these tumor cells become resistant?

So the approach that we’ve been taking is first to start by really trying to define the genetic basis of resistance in this context, and so we know that there has been real value in crisper screens. But I think increasingly we’re very excited about the possibility of circulating tumor DNA sequencing as well as potential for serial biopsies, particularly along this axis. As tumors gain resistance to combine genome sequencing as well as gene expression analysis to provide new insights into therapy resistance.
And we use a range of models, although from model organisms to mouse models to really get the mechanisms, and of course the ultimate goal is always to really be able to leverage the mechanism of resistance, ideally to come up with new therapies and so awhile. Of course we’d like these to be actionable were really particularly would like to go beyond that, would like to go beyond that, and to be sure to consider based on our mechanistic studies, what can we bring to the table in terms of stratification?
And today I'll talk about an example where we really think that we have to consider Bracco one patient separately from bracket two patients. Of course it would be best really if we can develop new biomarkers that will further help us stratify patients based on the mechanisms underlying resistance, and I think one real potential there is for example, circulating tumor DNA may allow us to identify patients who have a so called reversion allele. That'll now make them insensitive Department of Therapy.
and that baby one cohort, but there may be other patients where resistance is arising through a secondary mechanism that maybe. Therapeutically actionable and so I just wanted to take you through the work that we’ve been doing, just not just my lab, but across our team to look at the genetic basis of resistance. So much of again, these crisper screens have been published. The work that’s been going on here at Yale really has taken advantage of a partnership that we already have.
between Astra Zeneca and our team, particularly Ryan Jensen, and Ryan has been modeling reversion alleles that are arising from patient derived DNA sequencing. And testing really, is there still an actionable approach that we could use in these contexts or not? By functionally characterizing the reversion alleles? What I’m particularly excited about at the moment is that paleru so has been leading a trial along with Kurt Shopper, at the moment is that paleru so has been leading a trial along with Kurt Shopper, who you’ll hear from in a moment where she is and acquiring these serial biopsies. Along this progression to relapse.
And this allows us now to go in and really look not just a genome changes, but gene expression changes. And so these sequencing is ongoing at the moment, and we're really excited about the new targets that it may reveal. So it's well established that Braca one of its key roles is to promote...
what’s called double strand break and resection through the EXO 1 pathway. And this is a critical step in the HR pathway and so it was came out of these screens. That loss of either 50 BP one or Rev 7 can drive therapy resistance in the context of Graco one mutations. Well, my group discovered is that these are negative regulators of the bloom helicase acting with DNA 2, which is an alternative and resection mechanism. So this is a way where these tumor cells have essentially rewired reception so they’re no longer dependent on
bracca one and instead can use this bloom pathway and so as examples of what that mechanism has brought in terms of the way we’re thinking about future therapeutics, the first is that identifies the bloom helicases, a really novel target that we have already shown in vitro is also synthetic lethal with Bracco one on its own. Particularly if we think in the short term, maybe more actionable input ways in which this has changed. Our thinking is that it highlights also the potential for combinations.
of PARP inhibitors in ATR inhibitors, and that’s because the other thing we discovered is that this blue mediated helicase is driving resection at very high rates and this leads not just to functional reception to do repair. It actually leads to hyper resection, and ATR is an important negative regulator of resection, and so we think that this combination of treatments will push this. Hyper resection even further, and this is a really good rationale for why. Initially patients with RK one mutations may not respond well to a combination with an ATR inhibitor,
but when there is a mechanism that down regulates these particular proteins that will make these tumors very sensitive to the combination, currently just submitting anello I with paleru so where we are proposing to do a trial specifically in Bracco in patients because this is not a mechanism that’s relevant for the bracket, two patients. Hoping to really test this idea clinically, so thank you and I look forward to the questions.
much of this work as I mentioned was a collaboration with Astra and is also supported very generously by the Great Foundation.

Next, I'd like to introduce Jinyoung, he’s an associate professor of pathology and director of our Epigenetics program here at Yale and will be talking about epigenetic mechanisms of resistance.

Thank you, Barbara. On So, uh, my expertise in the menu on cancer genetics, and as you all know I project magnet is critical for cancer initiation and progression.
Especially my laptop is interested in understanding how epigenetic regulators, also called reader writer and erasers of being an maceration histone modification. How regulate different steps of cancer progression? My number to your interest in a couple different areas? One is resistant mechanism to anti cancer drugs, which is the main topic today. Cancer metastasis and tumor in valuation, which is one of the areas that I could show but will talk more about later on and next.
My #2 is also very interesting, developing different epigenetic drugs and we have done some work with your Center for molecular discovery, which is our in house training center and I have done some work with the NCI Experimental therapeutics program and right now I’m also collaborating some about tech and pharmaceutical company in this area as well and in the next 2 slides I’m going to tell you some of the examples that we have done to look at the resistant mechanisms. One which is targeted therapy,
and in this case the transaction number one called Herceptin for breast cancer, and we can generate those resistant cells in tissue culture. And we found that those resistant cells actually are do not have genetic mutations. They actually resistant mechanism is actually reversible if you take the drug away from the cells for short period time and they are still maintain resistant. But if you take it away for a long period time, for example about months and those cells becomes those so called watch out.
And those cells become sensitive to local internal mechanism next piece. We profile the expression of the reason compared to the sensitive cells. We can see that those resistant cells have increased oxidative phosphorylation or called off force and remarkable need. Those cells are very sensitive to ox force inhibitor. As you can see the tumor regression if you combine traditional Antonio Massenet you combine traditional Antonio Massenet which is 1 nautical force inhibitor. You can see regression of those. Resistant tumors Next place as I
00:30:59.744 --> 00:31:02.752 mentioned that this app is genetic

00:31:02.752 --> 00:31:05.667 mechanism that contributes to resistance,

00:31:05.670 --> 00:31:07.990 so we are one of the mechanism we

00:31:07.990 --> 00:31:10.498 found is that Arcadian 5 histone

00:31:10.498 --> 00:31:12.813 demethylase are critical for this

00:31:12.813 --> 00:31:14.873 formation of those resistant cells

00:31:14.873 --> 00:31:17.153 we can combine with the target

00:31:17.160 --> 00:31:19.224 therapy and Kaden 5 inhibitor which

00:31:19.224 --> 00:31:21.989 this is one of the early generation

00:31:21.989 --> 00:31:24.629 inhibitor and four to prevent the

00:31:24.629 --> 00:31:26.891 formation of the recent sales for

00:31:26.891 --> 00:31:29.042 both breast cancer which is beating

00:31:29.042 --> 00:31:30.610 for some report cells.

00:31:30.610 --> 00:31:34.586 And non cancer cells on PC 9 cells.

00:31:34.590 --> 00:31:36.111 And next race.

NOTE Confidence: 0.693806850910187
So we are also very interested in understanding how resistant happens to our email checkpoint blockade and this is our version of the cancer immunity cycle and and as you can see, there's actually 2 steps are the critical for email checkpoint to work is the trafficking and infiltration of the immune cells to the tumor and apparently some of the epigenetic modulators have been shown to be critical for those processes, and then I will just show example in our laboratory next please. Where we found the Canadian
Fire B or history, history.

You must nice file B is critical off for.

Infiltration and trafficking of the T cells to the tumors.

And if not colocating 5B,

which is more smaller,

generated by Markus Persson.

Book idea we can see that if you

ockout account info be those

cells are unable to form tumors.

And if we re challenge,

those are two mice with control sales,

which normally grow very well.

You can see they cannot grow and
meaning that those might have gained immunity against those younger cells.

If you look at the young one point cells down in the policy, you can see those cells are not responsive to PD one blockade at all. And if we do need killing file before those cells, you can see the slowdown of the growth and if you combine with PD one blockade you can significantly extend the lifespan of those miles.

So this suggests that can you invite me is that very good target to overcome resistance to email,
check one blockade and I would just want to mention that this is done in collaboration with multiple laps and yell, including archical, even sucking and much boesenberg snap. So team science is one of the same idea. We workout together or not. Thank you. Thank you that is such a terrific story. Now I'm pleased to introduce Curt Shopper. He’s an assistant professor of pathology and medicine. An recent rooms at the end of an NCI Merit Award. He conducts really cutting edge
imuno profiling studies and
NOTE Confidence: 0.769105613231659
look forward to your talk Kurt.
NOTE Confidence: 0.648846089839935
Thank you, Barbara. Next slide please.
NOTE Confidence: 0.825054228305817
So I trained clinical molecular
NOTE Confidence: 0.825054228305817
diagnostics that I've been working in
NOTE Confidence: 0.825054228305817
cancer immunology for about 10 years now,
NOTE Confidence: 0.825054228305817
and it's unquestionable that immuno
treatment of cancer.
NOTE Confidence: 0.825054228305817
But there are major challenges
NOTE Confidence: 0.825054228305817
still to overcome,
NOTE Confidence: 0.825054228305817
so I'll cover a few of the challenges
NOTE Confidence: 0.825054228305817
that I think are critical to
NOTE Confidence: 0.825054228305817
potentially move the few forward,
NOTE Confidence: 0.825054228305817
one of which is that I think there
NOTE Confidence: 0.825054228305817
have been conceptual limitations
Relative to drug development, I think the focus of many people developing targets has been on immuno stimulation, but that doesn’t necessarily consider correcting alterations in the tumor and this is critical because if we’re only stimulating T cells we are and there is not a clear gradient towards activating it more in the tumor. It’s likely that the therapeutic index is smaller and the potential benefit and toxicity balances is affected. So I think the concept is that we shouldn’t
focus only on stimulating T cells everywhere.

We should probably look for.

Signals that have a gradient favoring the tumor in relative to the development of biomarkers for resistance.

I think there have been a little bit of confusion in the field because it mean a therapy has been used so widely that people are calling every patient that don’t respond as a resistance.

And conceptually I think that’s probably not accurate because patients without PD L1 expression tumor mutational burden.

any biology should not respond to start with, so I think there is a confusion between.

Any patient that Blacks benefit
versus true resistance, which in my opinion are the patients that should have responded but didn’t. I think this is critical to design programs and biomarker plans. The second important concept that it’s connected with the previous one is that it’s probably necessary to identify dominant immunization pathways that are well represented. The tumor and this is for the same reason because we need to have this gradient and strong biology in the tumor to be able to. Achieve a meaningful anti cancer response.
and then another major need in the field is trying to identify potential targets that are beyond the T cells. So to have complementary effort and not have only redundant mechanisms, another important observation is that we as I follow you know when we look at the tumors we realize how difficult and how complex is the tumor microenvironment. Where most interactions between tumor and immune cells are happening. And I think the suffering. The tumor microenvironment and how different it’s a major need to really drive better biomarkers and better immunotherapy.
Then also I think we need to do a better work at understanding the interactions between major dominant oncogenic signals and immune evasion pathways. This has been somehow being revealed in EGFR mutant tumors that are less sensitive and less inflamed, but they I think there’s a whole world to discover. What alterations in the tumor, somatic alterations are able to manipulate. It means an immune response. And then finally, I think there are limitations of traditional studies as we just solve from Jane.
Many alterations are not at the genomic level. Which is the favorite way we used to analyze the tumor site of the interaction. So I think by just doing genomic analysis, we're missing a lot of alterations that the immune system and this. I think it's something we can overcome and finally think that most of the studies are focusing on both ends on the very early discovery type of work, with crisper screens and other strategies. And then there is a huge effort on the clinical development, but I think there is room to improve some studies in more sort of human real context.
So this is an example of the approach that we have taken in my group where we generate hypothesis using discovery in biology and then we actually have generated assays to screen for pathways, cell types in tumor cell indicators in the same issue.

So we can actually do both genomic analysis to understand the genomic context during drivers, but then we can also look at the immune contexture and pathways that are potentially actionable. We have become pretty good at looking at multiple.
High throughput methods to detect protein level and then we can do single cell analysis, spatial analysis and really try to understand the tumor microenvironment to prioritize what signals are dominant or relevant, we usually use aggressive analysis using outcomes and response to treatment. So that way we can identify which signals are relevant from the ones that are not next slide please. This is important because ultimately those signals are the ones with. Then we can validate in vitro to demonstrate that these are not just
00:39:12.381 --> 00:39:13.539 epiphenomenon’s or correlations,
NOTE Confidence: 0.826502799987793
00:39:13.540 --> 00:39:15.375 but they are mechanistically relevant
NOTE Confidence: 0.826502799987793
00:39:15.375 --> 00:39:17.757 and then ultimately we can go back
NOTE Confidence: 0.826502799987793
00:39:17.757 --> 00:39:19.444 and look at this in the context
NOTE Confidence: 0.826502799987793
00:39:19.444 --> 00:39:21.009 of human clinical trials,
NOTE Confidence: 0.826502799987793
00:39:21.010 --> 00:39:22.960 and I’ll show you an example
NOTE Confidence: 0.826502799987793
00:39:22.960 --> 00:39:25.600 of that next slide, please.
NOTE Confidence: 0.826502799987793
00:39:25.600 --> 00:39:28.379 So just for to illustrate how this
NOTE Confidence: 0.826502799987793
00:39:28.379 --> 00:39:31.568 cycle works, this is a story that it’s,
NOTE Confidence: 0.826502799987793
00:39:31.570 --> 00:39:34.013 uh,
NOTE Confidence: 0.826502799987793
00:39:34.013 --> 00:39:35.863 have published this year where we
NOTE Confidence: 0.826502799987793
00:39:35.863 --> 00:39:37.723 identify Interleukin 8 and local
NOTE Confidence: 0.826502799987793
00:39:37.723 --> 00:39:39.425 neutrophils in the tumor micro
NOTE Confidence: 0.826502799987793
00:39:39.425 --> 00:39:41.517 environment as dominant immunization
NOTE Confidence: 0.826502799987793
00:39:41.517 --> 00:39:44.322 pathway and resistant mechanism.
NOTE Confidence: 0.826502799987793
So the story started a few years ago where we looked inside too. We found that Interleukin 8 was producing tumor cells and highly associated with resistance to immune checkpoint blockers. To advance this further, we looked at the relationship between Interleukin 8 and neutral fields as shown in the upper side of the slide, and we found a fraction of tumors that had up regulation of Interleukin 8 and an unfavorable microenvironment characterized by increased deals in fewer T cells. We also did genomic analysis to
00:40:17.310 --> 00:40:18.992 understand that this was independent

00:40:18.992 --> 00:40:20.684 from tumor mutational burden

00:40:20.684 --> 00:40:22.376 and major genomic alterations,

00:40:22.380 --> 00:40:24.414 and then we finally were able

00:40:24.414 --> 00:40:25.770 to demonstrate that the

00:40:25.834 --> 00:40:28.198 production of Interlake in the tumor.

00:40:28.200 --> 00:40:29.960 was actually associated with

00:40:29.960 --> 00:40:32.160 interleukin 8/IN serum in circulation,

00:40:32.160 --> 00:40:34.918 so we that we conducted an studying

00:40:34.918 --> 00:40:37.774 over 1200 cancer patients from three

00:40:37.774 --> 00:40:40.960 phase three pivotal trials using immune

00:40:40.960 --> 00:40:43.462 checkpoint blockers and we found that

00:40:43.462 --> 00:40:46.240 about 1/3 of a patients across tumors

00:40:46.240 --> 00:40:48.880 have up regulation of interleukin Aiden.

00:40:48.880 --> 00:40:51.440 They have low sensitivity to

NOTE Confidence: 0.8223637342453
immune checkpoint blockers.

Then to further demonstrate this, we need another study in which we cultured neutrophils and my Lord arise suppressor cells to show the mechanism behind and we were able to demonstrate that formation of Nets was involved in affective response suppression, and then ultimately we’re working with the clinical trial where patients are being treated with an antibody and targeting Interleukin 8, and to understand if this pathway can actually be action in real patients, and hopefully we can use the biology
that we figure out to drive.

The biomarker plant next slide please.

So finally we have gotten a little bit

more sophisticated now and generated

models or in in vitro tumor treatment.

And this is just an example of what we’re

doing where we can culture primary tumors,

and we can then generate preparations and

analyze the tumor micro environment.

Change now perturbing these tumors

with immunostimulatory or other

anti cancer agents and we are

incorporating new technologies such

as single cell transcriptomics.
Another analysis to do more unbiased studies.

Thank you,

Thank you Kurt. I mean I think probably everybody can see the incredible power of that approach.

Well, we said at the outset, Yale engage is focused on building bridges and collaboration with industry, and in each of these seminars, we've invited an industry partner to speak to us, and I'm really thrilled that today, it's Susan Galbreath she's a senior vice president and head of early oncology R&D and Astra Zeneca. She's been there about 10 years and.
In the early development program, there brought 7 compounds into phase three. The story with PARP inhibition, the third generation EGFR inhibitor. Awesome Merton if that our colleague, Roy Herbst, was involved in presenting very impactful angemon trial this year. Megan met inhibitors selective estrogen receptor directed agents. Really phenomenal portfolio and a phenomenal track record of success.

So Suzan, we look forward to hearing your thoughts.

Thank you, Barbara Ann. It’s a pleasure to be here.
with you and just a bit introduction. I’m a clinical psychologist by training MD PhD and I’ve been, as Barbara said, Astra Zeneca for 10 years and before that I was in the US with Bristol Myers Squibb also in the early Development Group and stayed there for about 9 years. Just go on to the next slide. I want to talk a little bit to build on some of the thoughts we’ve got about, you know, understanding resistance and one of the challenges that we’ve got about understanding resistance is really having access to the samples. That would enable us to understand.
the clinical resistance.

So Katie Elite is already talked to you about some of the models that we can use preclinically to model resistance. One of the challenges we’ve got with those techniques though, is that it doesn’t always predict what the true prevalence of the resistance mechanisms is going to be in the clinical setting. So if you start off with a PC 9 so when you look at the mechanisms you don’t necessarily understand what the true prevalence of all the
things are when patients are starting with their own set of Wiring diagrams in their EGFR mutant lung cancer. The other challenge that you’ve got is tried for number of years to actually get biopsies from patients on at the time of progression in clinical trials, or must we concluded that you know typically has to be as an optional biopsy. At that time of progression, we’ve actually heard across the range of clinical trials. Relatively few of those actually materialized, and so that means that our mechanisms
00:44:45.543 --> 00:44:46.813 of understanding resistance during
00:44:46.813 --> 00:44:48.278 the development of certain IP,
00:44:48.280 --> 00:44:50.110 you know, have been somewhat limited.
00:44:50.110 --> 00:44:51.976 We started right the beginning by
00:44:51.976 --> 00:44:53.480 looking at circulating tumor DNA,
00:44:53.480 --> 00:44:55.316 it right from the phase one
00:44:55.316 --> 00:44:56.540 Trials with awesome antonym,
00:44:56.540 --> 00:44:58.484 and we have some understanding of
00:44:58.484 --> 00:45:00.109 actually published some of the
00:45:00.109 --> 00:45:01.729 data from the first line study
00:45:01.729 --> 00:45:03.534 with a semantic that flora trial
00:45:03.534 --> 00:45:05.406 looking at those CT DNA mechanisms,
00:45:05.410 --> 00:45:07.348 but really actually one of the
00:45:07.348 --> 00:45:09.390 things that comes out of that is,
00:45:09.390 --> 00:45:10.502 we could only explain.
I am just over 1/3 of the patients resistance mechanisms through looking at city DNA and the patterns that we saw there was we saw their city. The emergence of the Sistine 797 S mutation met amplification PSP KEARNEYS pathway mutation. An activation fee 10 losses and in some cases and MEK pathway activation as well in some cases. But the really the majority of patients we still had a question mark over what the resistance mechanisms worth. So that led us to design that this kind of study. It’s called the Orchard and platform study.
This takes patients that we’re progressing on. First line automotive, and it offers them something that is potentially of benefit to them, which is to take a biopsy to look at what the data says on next generation sequencing. From that biopsy and then to allocate them to a range of different potential arms and this biomarker matched arms which you can see above depending on the mechanism that that is seen with resistance. And then there’s also non biomarker match on.
And this has been an important component of many platform trial designs because it means that every patient whose given a consent to have a biopsy gets the offer of something. I can’t guarantee that than what they’re getting offered is necessarily going to work, but it gives them that, and that has driven really quite a good uptake in terms of enrollment and accrual in this. And actually, what one of the things that we’ve already learned now is, we’ve now got, you know, data and over 60 patients.
NOTE Confidence: 0.818565964698792
00:46:44.106 --> 00:46:46.770 with tissue available at the time of
progression in the Orchard study,
and now that we can have an
identifiable resistance mechanism now,
in nearly 2/3 of patients,
as opposed to just a third.
We’ve increased the detection and
some of the amplification mechanisms
which can be underestimated using
CT DNA would increase the detection
of some of the Fusion mechanisms,
which can also be difficult to
detect using the CT DNA techniques.
And we’ve got a better sense,
With the prevalence,
there's still some work to be done here, and I still think we need to look at the epigenetic mechanisms that are driving resistance in this setting, but I just wanted to illustrate this as an example of one way that we need to look at in terms of understanding, documenting resistance and moving on from it so we can go to the next slide. The similar approach has been taken in the understanding.

Resistance to checkpoint inhibition, and I completely agree with shoppers comment, but not everybody who progress is on a checkpoint inhibitor is necessarily truly resistant,
but I think we need to understand some of those mechanisms, and again, this is a mechanism where you can get the biopsies from these patients. Also, some peripheral blood sampling and look at ways in which we can potentially offer them. Treatments that may have the opportunity to make a difference. I just want to share with you a couple of observations from this.
there are some mechanisms that we might anticipate seeing based on, you know, really good data that’s already emerged, and this is about the loss of her Psycho City for HLA or MHC and we are seeing as expected. But after treatment or one of these checkpoints, inhibitors and increased prevalence of loss of HLA or MHC. In the inability of the tumors to be seen by an an an an effective by at the adaptive immune mechanisms of if the antigen can’t be presented effectively, it’s like.
Other things that we're doing.

We've seen a range of different mechanisms that we have.

Wilson mentioned the fact that obviously we're looking at the ATR combination with a lap robe in terms of part resistance,

but in fact actually one of the observations that we made earlier phase one with our selected slot assertive,

which is, uh, ATI inhibitor,

is that we were seeing some unusual responses in patients that had a prior checkpoints in innovation.
In some other trials, and so that led to some further investigation and so there are certain underbelly map is one of the arms in the Hudson study and some of the data that we’re seeing is quite interesting in seeing that. Getting a decrease in exhausted T cells, exhausted NK cells and an increase in antigen presentation in patients that have both got primary resistance to checkpoint inhibition and subsequently had some degree of response and subsequently progressed as well. And we’re also seeing it not just in the ATM mutant patients that are selected,
but also more broadly, so.
This is just an interesting observation.
There's a lot more mechanistic data that is required and that will be followed.
But I do think that these kinds of trials are really helpful in trying to understand the clinical prevalence of resistance.
Mechanisms get a lot more data that can feedback, and you know, back with the preclinical work that we can do to them to then understand what we might do next.
So I'm going to stop there and
I’m very happy to address any questions that you might have.

Thank you.

That was fabulous. Thank you very much.

I am now going to ask all of the panelists turned on their audio and video and will now go into the full discussion.

And I’m going to ask the attendees to please continue to post questions we are monitoring these and the first one, I think.

Basically immediately follows that the last slide that we saw and so maybe I’ll ask Susan and Kurt both to address this.

How critical is it to overcome the mechanical functional barriers to immune
checkpoint inhibitors and the question relates specifically to HLA loss, although I can think of other mechanisms related to hypoxemia and vascular alterations as well, but can you please comment on? Potential pathways and targets to overcome mechanical and functional barriers to immune checkpoint inhibitors and Susan. Do you want to go first and then kick it to Kurt? Yeah well, the Council think of when I think of 1st when you’re talking about mechanical barriers potentially is pancreatic cancer.
Cause at the high level of you know Disney plastic streamer that you see that has been discussed as not just having actually a physical potential barrier to treatment but also the presence of the constituents of that. Desmond plastics. German may also have a you know, biochemical effects that reduce the likelihood of sensitivity to. Of the tumor cells that are adjacent about two treatment, and I think there are a lot of data suggesting that understanding the components of the micro environment, the distribution and types of you
00:52:27.618 --> 00:52:29.070 know cancer associated fibroblasts,
00:52:29.070 --> 00:52:29.798 for example,
00:52:29.798 --> 00:52:31.618 and not in that disease,
00:52:31.620 --> 00:52:33.906 and their feelings that might be
00:52:33.906 --> 00:52:35.430 absolutely critical to understanding
00:52:35.492 --> 00:52:37.757 mechanisms of resistance and sensitivity.
00:52:37.760 --> 00:52:41.158 I think in the context of loss of HLA.
00:52:41.160 --> 00:52:43.552 It it’s you know that you know lots
00:52:43.552 --> 00:52:46.333 of HLA may increase the sensitivity
00:52:46.333 --> 00:52:48.968 potentially to other mechanisms like
00:52:48.968 --> 00:52:51.366 inducing the innate immune system
00:52:51.366 --> 00:52:54.060 rather than the adaptive immune system
00:52:54.060 --> 00:52:56.210 to NK cell enhancement potentially.
00:52:56.210 --> 00:52:57.722 Then you know so.
00:52:57.722 --> 00:52:59.990 So there are things that then
96
creates a formability I suppose.

I think the issue from my perspective is it you know you wouldn’t be expecting.

No high likelihood of subsequent response to something that requires fundamental mechanism,

so we should be segmenting patients by an understanding of these mechanisms in order to identify the populations that might best be subsequently treated with different kinds of therapies.

Cut any thoughts from you.

Yes, I agree with all the comments.

I think there is more biology emerging
suggested that the mechanical barriers may not be so mechanical. You know some of these fibroblast basic read inhibitory molecule so it may be also an active immunity victory component to that and that I think is driving. I think they were going to see a lot of new studies showing active mechanism of rejection of immune cells in the tumor bed and relative to the empty in presentation. We have actually a study under review that should see the light soon. When we look at large cohorts of tumor mapping, different parts of the antigen presentation
pathway in a Long story short where we’ve learned is that when we look at the genomics, we don’t see that. So the majority of alterations are non genomic meaning non mutation related. In the second interesting lesson is that depending on what molecule is lost in the tumor cell meaning HAHABCV, A2M or other proteins, the immune contexture changes. So so I think. Understanding that part will be critical to understand how to treat those patients, we do see upregulation of natural killer service in in certain loss. Eventually molecules,
but not in everyone, and each of them has sort of a certain different balance between T cells, NK cells, and other cells. So I think it will be critical to do those studies to understand how granular disease and if we can lump the antigen presentation defect into one category. Or maybe it will be more than that. I think that’s to be figured out. So just continuing on with this theme in a question for Chin can HLA loss be overcome by epigenetic modification? Or what is epigenetic role in HLA loss? So this is not an area I have been
working on very well having it, but I could just mention another with those changes are non genetic changes so we have different tools to execute those jeans. Reactivate those jeans and to make them successful too. Make make them to be sensitive So email checkpoint blockade will work if you re reactivate those. Terrific terrific, I have a question that was submitted earlier, but I think. Could probably be answered extensively or exhaustively by each one of the panelists, but maybe I’ll ask Katie and
00:56:06.702 --> 00:56:08.989 Mark to start on this one.

00:56:08.990 --> 00:56:11.454 How does the mutational landscape of a tumor affect resistance and sensitivity?

00:56:11.454 --> 00:56:13.479 And I’m interpreting that the questioner means the other mutations besides the one in your target molecule.

00:56:17.919 --> 00:56:19.840 I think this is really an area that we are starting to learn more about as we have learned more about the mutational profiles of tumors and of different genetic subgroups of tumors.

00:56:22.170 --> 00:56:24.350 Thank you sure I can.

00:56:24.350 --> 00:56:26.960 I can get started with that.

00:56:26.960 --> 00:56:29.696 I think this is really an area that we are starting to learn more about

00:56:29.696 --> 00:56:32.587 we are starting to learn more about

00:56:32.587 --> 00:56:35.834 as we have learned more about the

00:56:35.834 --> 00:56:38.966 mutational profiles of tumors and of different genetic subgroups of tumors.

00:56:41.348 --> 00:56:44.470 So now one of the things that we’ve been able to look at,
for example, are in if we think about lung cancers in different oncogenic driver subgroups.

We can look at the pattern of occurring genetic alterations that happened, for example, in K Rasputin lung cancers, these can occur with P53 mutations.

They can occur for example with mutations in STK 11, also known as Elchibey one.

And we’re really beginning to learn about what it means.

If the tumor has Akira’s mutation and a P53 mutation versus ACARAS mutation.

And then Elchibey one mutation for example.
And what and that the LKB one meeting tumors seem to have a different or reduced sensitivity to immunotherapy treatment, for example, and.

In parallel, we’re really starting to scratch the surface and really beginning to understand how different Co occurring alterations also impact response to targeted therapies.

Some of the work that we’ve been doing recently looking at different tumor suppressor gene alterations
in EGFR mutant lung cancer and how they affect sensitivity to tyrosine kinase inhibitors. One of the things that has emerged from our studies in animal models, an also is emerging from studies of patients. Patient specimens is that if you have EGFR mutant tumors that also have mutations in the keep one access, so the keep 1 NRF 2 access that is important for the antioxidant response of a tumor cell. If you have mutations that Co occur in that path where you have a decreased sensitivity to tyrosine kinase inhibitors, so the tumors will shrink.
These targeted therapies, and so that begs the question, is that a subset of patients who you could, for example, select initially for treatment with different therapies, or for combination therapies together with a tyrosine kinase inhibitor so that you could. Improve outcomes in patients with that disease. I think of course, these types of landscapes also this studying these landscapes.
really requires a lot of mechanistic investigation to understand exactly what is happening in those tumors. Finally, I think one of the other things to think about in terms of the genetic landscape also has to do with the overall mutation burden and the overall tumor mutation burden, which. You know we talk a lot about it in the context of immuno therapies and where you know we’ve. We’ve heard about a lot about it in recent years. I’d say also there’s some evidence that in the context of targeted therapies,
the overall genetic landscape or the tumor mutation burden can have an effect on the response to targeted therapy. So again in EGFR mutant lung cancer tumors that seem that have that are in the highest tertile of tumor mutation burden, which is generally lower than most other lung cancers. But in that highest circle seemed to do worse on treatment with targeted therapies with tyrosine kinase inhibitors and the ones with the lower two mutation burden. So there are lots of different
aspects to consider.

The specific mutation.

So qualitatively but also quantitatively.

Yep,

I was just at the office or at a kind of.

Broad conceptual thought to

that which is ultimately,

I think, with all of these,

with all of the therapies.

We’re talking, one is really

trying to correct the signaling network.

However you define network,

whether its intracellular intra tissue,

Inter intra Organism.

Once regular network and in a sense

if you think about the fact that
cancers are really caused by the networks losing robustness and kind of careering out of control to uncontrolled proliferation so far. It’s almost surprising actually. The targeted therapy can work, and indeed, actually, if you create models where you just mutated something, we’re hitting with a targeted therapeutic and nothing else. You don’t actually. But that’s not enough to cause cancer, so the context is key, and the targeted,
01:01:17.217 --> 01:01:20.830 the target that we’re trying to correct is.
NOTE Confidence: 0.625242710113525
01:01:20.830 --> 01:01:22.714 It’s really just kind of an
NOTE Confidence: 0.625242710113525
01:01:22.714 --> 01:01:25.085 Achilles heel in the sense for the
NOTE Confidence: 0.625242710113525
01:01:25.085 --> 01:01:27.179 rather plastic tour in some sense,
NOTE Confidence: 0.625242710113525
01:01:27.180 --> 01:01:29.620 so I think I think that the answer
NOTE Confidence: 0.625242710113525
01:01:29.620 --> 01:01:32.175 the answer to the question is that we
NOTE Confidence: 0.625242710113525
01:01:32.175 --> 01:01:35.189 need to think about these things as networks.
NOTE Confidence: 0.625242710113525
01:01:35.190 --> 01:01:37.176 We need to get into considering
NOTE Confidence: 0.625242710113525
01:01:37.176 --> 01:01:38.870 the systems biology of this.
NOTE Confidence: 0.625242710113525
01:01:38.870 --> 01:01:40.868 I think there are two ways
NOTE Confidence: 0.625242710113525
01:01:40.868 --> 01:01:42.540 of thinking about that one,
NOTE Confidence: 0.625242710113525
01:01:42.540 --> 01:01:44.964 and you’ll be aware of this as the
NOTE Confidence: 0.625242710113525
01:01:44.964 --> 01:01:47.220 enormous effort put into machine learning,
NOTE Confidence: 0.625242710113525
01:01:47.220 --> 01:01:48.544 AI types of approaches,
NOTE Confidence: 0.625242710113525
01:01:48.544 --> 01:01:50.890 whereas we collect more and more data.
NOTE Confidence: 0.625242710113525
01:01:50.890 --> 01:01:52.440 For the mutational landscape to
try to understand their with various their principle components, analysis and what have you, what. How we can correlate combinations of mutations with sensitivity and so on so forth. But there’s another element I think we have to consider the a variety of systems biologists are taking, which I think is really key. And actually I think RAF inhibitor resistance illustrates this very nicely. Is that we we can actually learn an awful lot about how the networks operate, you know?
A classic example is if you ever ask mutation, then the graph inhibited does the wrong thing, you know, but the bottom line is I think that we really we need to start thinking beyond the targets to the networks and what the effect of the targeted therapeutics is on the networks and that of course is going to hold in the immune context too because again what you actually correcting as curtain Susan pointed out as as you’re actually dealing with, that is,
01:02:48.802 --> 01:02:50.930 is trying to restore balance in an incredibly complicated interstellar the network.
01:02:50.984 --> 01:02:52.808 So I think there’s a couple of perspectives I would like to.
01:02:55.022 --> 01:02:56.530 Could you just answer that by introducing people a little bit to what’s going on at the Systems Biology Institute.
01:03:01.132 --> 01:03:03.190 Not all of the audience may know about the scale of the effort.
01:03:03.190 --> 01:03:04.999 Yeah indeed. So actually at yeah we have a system colleges too that’s headed up by Andra Chanco, who’s the Director of Vietnam.
01:03:12.300 --> 01:03:14.524 have a system colleges too that’s actually headed up by Andra Chanco,
NCI cancer Systems biology centers.

There's a NCI has a physical Sciences long college center that.

Actually, that initiative that you’re involved with one of those at Penn and and can sort centers consortia that 100 grand sent, Systems Biology Institute here is really very council focused. It has a lot of interactions and so the Systems Biology Institute here is really very council focused.

Andre is an integral part and Andre is an integral part and also on West Campus at Yale, and Andre is an integral part. and Andre is an integral part of the Cancer Center.

Of course, the Council biologist is too.
and so are most members of the Systems Biology Institute and the kinds of things. Being looked at there, which is actually related to this, so that Barbara it’s a good point are for example Andre is very interested in looking at. But it sells from brain tumors in particular and asking. Adam and looking at at migration versus proliferation in those cells, and the epigenetic difference between those in terms of what’s defining the signaling networks that cause the cells to behave very differently.
And he can do that with some microfabricated devices where you can separate cells based on how rapidly they can migrate and then go in and look with various single cell and other technologies to look at their transcriptome and obviously gentleman and epic transcriptome etc. So that’s really very exciting. There’s another element which is one of city channel that is doing an awful lot of work in terms of it in the system bars Institute. That is one of city channel that many of you will come across. City is doing an awful lot of work in terms of trying to understand.
using in vivo CRISPR technologies.

Origins of resistance to terminate therapies and another therapeutic approaches.

And so that’s really very exciting again.

Is plugged into the network consideration of what’s going on,

And then one other aspect,

which I think is really cool.

Actually as a project in our in EU 54

that Andre Valances that Gunter Wagner,

who’s an evolutionary biologist is

is very interested in why certain.

Mammals don’t tend to get meta

static cancer cows in particular.

As an example that caused him
not to die of cancer,

they just carry them around with the carry.

The tumors around with him without metastasize Ng,

and pretty much we don’t see them here because they all killed before they get to that stage for other purposes.

And so that’s fascinating.

The network differences between the mammals that do and don’t suffer from metastatic cancer, and actually.

It’s kind of related in some senses to placental invasiveness in some.
In these of these organisms, which kind of makes sense in some ways. And so. So there’s a cost, if any. There was a cost in some ways of having placenta that more interdigitate ihd, which is that you more susceptible to metastatic metastasis in your cancer. So these different perspectives, whether it’s immune. Immunology approaches targeted therapeutics. I think there’s a a burgeoning and is very strong at. Yeah, I’m really very exciting. I think a burgeoning effort and understanding of how to put
01:06:44.330 --> 01:06:45.926 this into the quantitative,
NOTE Confidence: 0.760184228420258
01:06:45.930 --> 01:06:48.290 and I think it needs to be quantitative
NOTE Confidence: 0.760184228420258
01:06:48.290 --> 01:06:50.380 in the sense of biochemical
NOTE Confidence: 0.760184228420258
01:06:50.380 --> 01:06:52.288 networks and pathways contexts.
NOTE Confidence: 0.822815236837968
01:06:53.940 --> 01:06:55.952 Wonderful. Oh, it’s perfect.
NOTE Confidence: 0.822815236837968
01:06:55.952 --> 01:06:58.970 I have a question here asking
NOTE Confidence: 0.822815236837968
01:06:59.059 --> 01:07:02.090 the panel to comment on the role
NOTE Confidence: 0.822815236837968
01:07:02.090 --> 01:07:04.988 of proteomics and studying tumor
NOTE Confidence: 0.822815236837968
01:07:04.988 --> 01:07:07.084 resistance, and maybe you’ll
NOTE Confidence: 0.822815236837968
01:07:07.084 --> 01:07:09.780 you’ll take that first mark in
NOTE Confidence: 0.796327888965607
01:07:09.780 --> 01:07:11.336 the market. Only relates
NOTE Confidence: 0.796327888965607
01:07:11.336 --> 01:07:13.670 exactly to what I was saying.
NOTE Confidence: 0.796327888965607
NOTE Confidence: 0.796327888965607
01:07:16.360 --> 01:07:18.790 My view is that. Biochemist,
NOTE Confidence: 0.796327888965607
01:07:18.790 --> 01:07:21.296 but my chemistry is defined by the
NOTE Confidence: 0.796327888965607
01:07:21.296 --> 01:07:23.182 component by the combination of

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components that you have and so and a lot of those are proteins. Of course, it’s not just proteins and that there are lots of other things too, but oh mix of various sorts are crucial for really getting a quantitative handle on an understanding signaling itself. Response to therapeutic have course therefore resistance, and I think there are two components of it. What is just at and I would just want to stress this one is just the I guess fingerprinting approach that one often sees with pretty and say what proteins are there in the snapshot?
What metabolites are there in Tableau makes sense in the snapshot. That’s one aspect and that can give you a lot of information but looking at changes in the proteome changes in the metabolon with time is really a crucial aspect is really that’s what what? What gives us a picture of the networks that we’re trying to correct and corral. When we’re targeting them in with all of therapeutics that that we discuss it and I just point out that there’s a quite a lot of activity on this at Yale, and one of the people recruited into the Cancer Biology Institute, for example, is yeah, Shane Lou.
NOTE Confidence: 0.796327888965607
01:08:34.260 -- 01:08:37.370 who has been doing a lot of work looking at,
NOTE Confidence: 0.796327888965607
01:08:37.370 -- 01:08:38.158 for example.
NOTE Confidence: 0.796327888965607
01:08:38.158 -- 01:08:38.946 Proteomic Lee,
NOTE Confidence: 0.796327888965607
01:08:38.946 -- 01:08:40.916 both snapshots and time evolution
NOTE Confidence: 0.796327888965607
01:08:40.916 -- 01:08:42.419 of protein contents.
NOTE Confidence: 0.796327888965607
01:08:42.420 -- 01:08:44.310 it is considered an employee,
NOTE Confidence: 0.796327888965607
01:08:44.310 -- 01:08:46.949 and you know it’s kind of interesting
NOTE Confidence: 0.796327888965607
01:08:46.949 -- 01:08:47.703 you really.
NOTE Confidence: 0.796327888965607
01:08:47.710 -- 01:08:49.978 if you look at any point,
NOTE Confidence: 0.796327888965607
01:08:49.980 -- 01:08:52.332 sells the effects on the protein
NOTE Confidence: 0.796327888965607
01:08:52.332 -- 01:08:55.151 were really not what you would have
NOTE Confidence: 0.796327888965607
01:08:55.151 -- 01:08:57.895 predicted based on on what you’ve lost
NOTE Confidence: 0.796327888965607
01:08:57.970 -- 01:09:00.554 in terms of of gene copies or gain.
NOTE Confidence: 0.796327888965607
01:09:00.560 -- 01:09:01.262 And Moreover,
NOTE Confidence: 0.796327888965607
01:09:01.262 -- 01:09:03.017 it’s important to note that
NOTE Confidence: 0.796327888965607
reaction is really pioneered.

This too that RNA seek data and proteomic data have substantial discrepancies,

and so and so that means also appreciate the proteomics.

Is really an important thing to add to all of this code.

Yes, so stay think I would like just to comment about the frustration of analyzing tissue level data without spatial resolution.

This is critical because as a smart pointed, we see a striking difference between our name protein which is becoming the rule more than the exception.

But second, the protein measurements and
any other like really is context dependent. So for example, just to give you a rough example measurement of K protein in any given sample, if it’s in the tumor cell, it means that you know. Tumors are proliferating if it’s in the immune cells means good T cells are expanding, so really I think having the possibility of looking at the proteins in the in the context of tissue organization, it’s critical for understanding what’s going on, and I think that’s a little bit when I
tried to reflect in my presentation, we're still early. We're getting more quantitative than throughput. It's coming up to speed, but I think it's an important dimension of the protein and any other light data. Absolutely perfect and Megan. Do you want to just jump in on this one as well? I just wanted to add just also OK, great. You know, as a first, just to say I think this is exactly right. When we asked us why, we know that just doing the genome
sequencing is not going to be sufficient.

We can start with the gene expression analysis because there are these epigenetic changes, but it’s very clear that that’s also in not sufficient.

And one thing I just wanted to point out is that as a cell biologist, I think we understand really well that for example, translational capacity is something that’s highly affected by stress, and so when we think about what’s going on in a particular tumor environment, how that might be affecting the.
Relative efficiencies of translation, which will never be fully reflected in an RNA seek data set, is going to be really important. And you know, one of the things, for example, that we think about a lot because hypoxia as a good example of this, appeared lasers work is thinking about hypoxia as a good example of this, and then the protein turnover aspects, right? And so these are all the factors that are contributing to what we might see different in a podium data set. And I was going to exactly the same point about,
you know, aneuploidy, because you know, we know, and this is particularly relevant also for DNA repair factors that one of the ideas of why aneuploidy causes such changes in the proteomes that. We have these large protein complexes which are very codependent and they become kind of out of titration with regard to the components and that can you know, most of us are working on complex molecular machines where that’s going to have an impact,
and so that's going to really require detailed, the kind of mechanistic analysis. But we might get pointed to the fact that we need to do that work only if we go actually looking for proteome wide data instead of just the genomics. Thanks great Katie.

Models actually represent a really useful system to look at signaling and challenges of studying the pathways in in patient specimens directly, all of the things that were brought up the patient arrived. Models actually represent a really useful system to look at signaling and
how signaling changes with treatment.

And it's one of the reasons for which we did engage in this effort.

In developing these models and also allows us to really explore how heterogeneous these samples are across different patient tumors so we can take tumors with a specific alteration or just across the wear resistant to specific therapy, and we can look at specific things in terms of at the protein level in those and we can look if we apply other therapies, what changes and so that really,
I think, is a very valuable system in which to study what’s happening at the protein level and signaling.

Susan, could I just ask you to comment on how the different omics are approached from within an organization like yours and and to what extent leveraging systems biology approaches is practical within your organization? Yeah, sure, and so I mean, I agree with the comments that have been made. First of all that we do need to look at these different mechanisms and it is possible to do that.
Increasingly, you know where we are looking with things like Multiplex immediate fluorescence at the spatial organization of the tumors, and in doing that in patient samples now. So I think the technologies are advancing to enable you to do that single cell sequencing. Is also helping. I think you know what I would say is that you can’t do that intensively on many child, so you have to choose the trial setting and the context for that. And it does have to be complemented by the kinds of things that Katie was talked about as well,
so I think you know you can. You can see some sense of the overall picture emerging from some of the clinical trial data you really need to understand the mechanism, and for that you need a different setting and. Environment to do that in the different techniques and then you know the the PDX models have some challenges the Gen models have their own set of challenges and I think what we can try and do is by looking collectively at at at,
The clinical sample data and these range of preclinical models and backwards and forwards across that divide, that's how you build up the bigger picture of understanding. But you know, I think it's like trying to sort of workout the overall picture from having several pieces of the jigsaw together, which is great, but you know nothing, that holistic view is absolutely critical to understanding, so I you know my comment would be that I think that the technology.
advances are now in place to enable us to see so much more than we were able to see 510 years ago. We need to bring that together, but have an integrated plan that goes across preclinical, translational and clinical trial environment. Then I think that’s critical, so we spend a lot of time in what is called early stage oncology without translation of medicine. group actually working with drugs and programs that are in late phase development already on the market like awesome Internet and you know. And if I’m out.
The other drugs that we have there because the two reasons one is that I think that’s absolutely critical to understanding how to develop those in and continue that. But Secondly that understanding their feedback into the discovery organization for new opportunities. And I think the final piece I would say is that we can’t do it all internally. Collaborations with organizations like Yale is absolutely critical. You’ve already heard a number of examples of the kinds of collaborations that we have that really helped to.
And to feed and stimulate the work that we're doing internally. So you know really appreciate the work that that Megan, a team of doing that Katie Ability and her team are doing because that sees what we're doing internally and we can't do all of it. Great good, there's a question here asking can we share examples of partnership with other academic centers that we may have for precision medicine efforts and adaptive combination treatment to overcome resistance and? And I'll talk about that maybe a little bit from the medicine side.
Pet Larusso here leads experimental therapeutics clinical trials network. Many consortium members and she and her colleagues are leaders in taking molecularly driven questions and actually molecular selection strategies forward in the Umm in the ETCTN network. Jeff Sklar, here, runs one of the Lamps that did the precision medicine sequencing for the match trial. We have investigators here leading match sub trials. We have, I think within our spores, collaborations across other cancer.
01:17:32.774 --> 01:17:34.678 centers that are molecularly
NOTE Confidence: 0.840360403060913
01:17:34.678 --> 01:17:36.659 driven clinical trial questions.
NOTE Confidence: 0.840360403060913
01:17:36.660 --> 01:17:40.988 So I think from the disease based and
NOTE Confidence: 0.840360403060913
01:17:40.988 --> 01:17:44.051 clinical arena Ann from the Phase
NOTE Confidence: 0.840360403060913
01:17:44.051 --> 01:17:47.490 one arena there is quite a rich.
NOTE Confidence: 0.840360403060913
01:17:47.490 --> 01:17:50.610 A network of of these types of interactions,
NOTE Confidence: 0.840360403060913
01:17:50.610 --> 01:17:53.368 I don't know if anybody wants to
NOTE Confidence: 0.840360403060913
01:17:53.368 --> 01:17:55.889 address more from the preclinical.
NOTE Confidence: 0.840360403060913
01:17:55.890 --> 01:17:56.530 Level.
NOTE Confidence: 0.786874294281006
01:17:59.390 --> 01:18:02.042 I could just just comment that the
NOTE Confidence: 0.786874294281006
01:18:02.042 --> 01:18:03.570 anaplastic lymphoma kinase work
NOTE Confidence: 0.786874294281006
01:18:03.636 --> 01:18:05.126 that I mentioned at work.
NOTE Confidence: 0.786874294281006
01:18:05.130 --> 01:18:07.140 That’s all guns are long term
NOTE Confidence: 0.786874294281006
01:18:07.140 --> 01:18:08.892 collaboration with people at Children’s
NOTE Confidence: 0.786874294281006
01:18:08.892 --> 01:18:10.974 Hospital in Philadelphia and a new
NOTE Confidence: 0.786874294281006
01:18:10.974 --> 01:18:13.232 pen where much of the computational
modeling is done actually through that.
And then another approach that
another aspect that we’re working on,
which is a collaboration of many.
Out of many academic medical centers
actually in the US and abroad,
we actually have through the Alex
is now in H Town Foundation and
approach to targeting Myc signaling.
Let me say it’s not targeting
Nick Per saver comes relates to
combination therapies and so forth,
the idea being that multigroup approach.
With the idea that that make aberrations,
particularly making neuroblastoma
affect the network, and in principle one could rescue the network with appropriate combinations, and I think with the technologies, as Susan pointed out, advancing, I think the time is right to get to ask that question in that type of way.

Anybody else wanna OK? There's a question here in the context of overcoming resistance. Can panelists share with their most excited about in terms of combination modalities? And maybe I'll just ask him to go first?
'cause I love the KTM Ivy story.

But I think everybody probably has their own favorite combination too,

and you just want to, yeah, so of course I think because I work samples next, my opinion might be any bias. Modulation is critical for that and not only the case. So one of the example I have showed this Acadian 5B where we can show pretty synergistic effect that you're going to check my blanket in multiple models.

I only showed one in breast cancer.
Will also see that as well. In addition, another's other modalities that you can actually modulate the tumor micro environment and, for example, someone that can recognize this as we are working on one, then it's called the CCR two, we can by inhibiting that we can change the macrophage population and by that, we can by inhibiting that we can change the macrophage population and by that, we can by inhibiting that we can change the whole tumor micro environment and make it sensitive for email, and make it sensitive for email, checkpoint blockade and this. This works well an intimate asks.
01:20:32.450 --> 01:20:34.598 Setting so I’m quite excited about

01:20:34.598 --> 01:20:37.339 that and that many of you probably

01:20:37.339 --> 01:20:39.399 know in other other institutions

01:20:39.399 --> 01:20:41.650 have studied with DMT inhibitors,

01:20:41.650 --> 01:20:42.450 HVAC inhibitors,

01:20:42.450 --> 01:20:44.450 and is it still inhibitors

01:20:44.450 --> 01:20:45.650 and those actually,

01:20:45.650 --> 01:20:48.198 I showed him assuming have showed strong

01:20:48.198 --> 01:20:50.450 efficacy in many different models,

01:20:50.450 --> 01:20:52.850 so I’m quite excited about this.

01:20:52.850 --> 01:20:54.450 This kind of combination.


01:20:58.202 --> 01:21:00.730 Anderson and Eli are broken.

01:21:00.730 --> 01:21:02.486 Working on demethylating therapy

01:21:02.486 --> 01:21:04.242 to uncover immune silencing

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and virally associated cancers.
And I think there are a lot of examples. I just wanted to come and I think that’s a very hard question, you know, because I think ultimately there the best combination is not going to be one combination that works every time I think it is so clear now that the tumors evade immunity through different dominant pathways and and more advanced tumors tend to have multiple pathways that I think the question has to do with where in an immunization pathways dominant and where more than one is dominant.
And I think that should drive the combination not think the opposite. Wait and think that one combination will fix tumors with different problems.

Yeah, so I think it’s very interesting that you heard that question as an immune resistance question. It was a very broad resistance question, but that’s an interesting perspective. I think one of the things that I think about sometimes is how some of the same mechanisms that have generated resistance to conventional therapies are now also generating resistance to immunotherapy and
how you know our relentless focus on target instead of environment, which you know? I think it’s something I’ve heard. You speak about alot. Kurt, you know we may have the same Achilles heel over and over again and in head neck cancer. A clear example of this is hypoxia, which leads to resistance to. It leads to resistance to. Radiation therapy. Prime example, but is now increasingly linked to resistance, demeanor.
therapy as well.

Yeah, and I say even taking it down to the simplest level of talking therapeutics it the answer is it depends because for example, just thinking about RAF inhibitor resistance. Actually David Stern and Marcus Bosenberg and others did a nice study that they published it a few years ago of combination combinations of drugs in a variety of cell lines for Melanoma and elsewhere. And showed that the combination which combinations work in which cells is very valuable and actually one of the things I'm quite excited about.
The moment we’re working as a group with systems biology island and equipment Los Alamos in the group and trying to understand that in terms of the signaling networks around RAF and MEK and rest in different cells, some cells from different cancers, and innocence. Which combinations work depends say on the level of KSR 1. And that’s a key determinant, and so it just depends on so much on how the network is wired, of course goes back to the question about proteomics, because ultimately that you’re
01:23:57.525 --> 01:24:00.172 trying to control the system and the way
NOTE Confidence: 0.769990742206573
01:24:00.172 --> 01:24:02.470 the system is set up by a chemically,
NOTE Confidence: 0.769990742206573
01:24:02.470 --> 01:24:04.622 it defines on how it will define how
NOTE Confidence: 0.769990742206573
01:24:04.622 --> 01:24:06.708 we respond to different combinations.
NOTE Confidence: 0.769990742206573
01:24:06.710 --> 01:24:08.798 And so I think we’re going to want
NOTE Confidence: 0.769990742206573
01:24:08.798 --> 01:24:11.406 to get into things at that kind of
NOTE Confidence: 0.769990742206573
01:24:11.406 --> 01:24:13.637 level to understand where we should
NOTE Confidence: 0.769990742206573
01:24:13.637 --> 01:24:14.860 use which combination,
NOTE Confidence: 0.769990742206573
NOTE Confidence: 0.769990742206573
NOTE Confidence: 0.769990742206573
01:24:17.641 --> 01:24:20.118 Got it that the case is going to be
NOTE Confidence: 0.769990742206573
01:24:20.118 --> 01:24:21.798 the case in the more complex systems
NOTE Confidence: 0.769990742206573
NOTE Confidence: 0.837461471557617
01:24:25.130 --> 01:24:26.420 And can I just add?
NOTE Confidence: 0.837461471557617
01:24:26.420 --> 01:24:27.976 There’s also the kinetic component, right?
NOTE Confidence: 0.837461471557617
01:24:27.976 --> 01:24:29.838 So I think when things were still
NOTE Confidence: 0.837461471557617
01:24:29.838 --> 01:24:31.817 not clear on is you better
NOTE Confidence: 0.837461471557617
01:24:31.817 --> 01:24:33.202 off with this combination early
NOTE Confidence: 0.837461471557617
01:24:33.261 --> 01:24:35.005 on or is this going to be better
NOTE Confidence: 0.837461471557617
01:24:35.005 --> 01:24:36.221 once you get initial resistance?
NOTE Confidence: 0.837461471557617
01:24:36.221 --> 01:24:37.763 And actually that’s may seem trivial,
NOTE Confidence: 0.837461471557617
01:24:37.770 --> 01:24:39.810 but I really don’t think it is and
NOTE Confidence: 0.837461471557617
01:24:39.810 --> 01:24:41.140 requires modeling to think about
NOTE Confidence: 0.837461471557617
01:24:41.140 --> 01:24:42.925 just how the kinetics is playing out.
NOTE Confidence: 0.844868659973145
01:24:44.450 --> 01:24:46.290 Great, related, related to that,
NOTE Confidence: 0.844868659973145
01:24:46.290 --> 01:24:49.640 one of the things that I was going to say
NOTE Confidence: 0.844868659973145
01:24:49.723 --> 01:24:52.907 is one of the things I’m excited about.
NOTE Confidence: 0.844868659973145
01:24:52.910 --> 01:24:55.682 Sort of going forward and looking at
NOTE Confidence: 0.844868659973145
01:24:55.682 --> 01:24:58.623 the field over the next few years is
NOTE Confidence: 0.844868659973145
01:24:58.623 --> 01:25:01.445 is really what we can learn about the
NOTE Confidence: 0.844868659973145
01:25:01.445 --> 01:25:04.510 tumor from the get go that can tell us
01:25:04.510 --> 01:25:07.327 how we would want to treat it to stave


01:25:09.840 --> 01:25:12.164 I think we’re starting to see some

01:25:12.164 --> 01:25:14.049 examples also of clinical trials

01:25:14.049 --> 01:25:16.094 that are starting to subset.

01:25:16.100 --> 01:25:17.955 Patients with certain tumor Gina

01:25:17.955 --> 01:25:20.179 types or whether tumors have certain

01:25:20.179 --> 01:25:22.611 features and sort of put them and and

01:25:22.611 --> 01:25:25.048 into trials with specific combinations,

01:25:25.050 --> 01:25:28.258 and I think that’s going to be really

01:25:28.258 --> 01:25:30.649 interesting approach in the next few years.

01:25:32.070 --> 01:25:33.198 Terrific, thanks, just

01:25:33.200 --> 01:25:35.090 a couple comments on this,

01:25:35.090 --> 01:25:37.502 so there’s a few things that

01:25:37.502 --> 01:25:39.532 you that you’ve heard there
that I just like to build on. A completely agree that we need to understand what’s the right combination for the set of what the adaptive mechanisms have been in that particular tumor, and I think to that end, looking at the adaptation at an earlier point than we typically do is a key part of this strategy, so there’s some really interesting. Concepts here that you will be working with Gordon Mills from OHSU on and looking at the adaptive rewiring that goes on which really happens quite quickly.
And of course one element of that that we need to understand is undoubtedly the epigenetic mechanisms that come in, 'cause they're quite commonly involved in some of the resistance mechanisms, and as I pointed out, we don't really have good techniques for looking for those if we haven't got a biopsy. Early on, so I think that's absolutely key, and then I think that also informs, but the potential for how we do combinations 'cause one of the limiting factors of actually getting these
to work has been the Talker ability of the combinations clinically.

And for that I think there’s a couple of chinks of light of what we can do.

First of all, we’re starting to develop some better tolerated therapies inherently, so I think that gives us a bit more headroom for some of the combinations that we need to do.

Things like Adcs, better ways of you know, delivering some of the mechanisms of killing give you a bit more headroom and understanding what drives total ability, and then looking at the sequencing.
rather than trying to do it does everything at the same time is another innovation that I think will come in that will help us with that. And but again I think we’re going to need to apply all of these tools that we’ve got and the modeling of that too, to reduce down the number of options that we actually bring into the clinic and increase the likelihood of each one of those being. Being successful with in combination therapy is going to keep us occupied for a little while yet before we solve that problem.
Terrific great well this I, I hope the attendees have enjoyed this exchange of opinion and knowledge as much as I have. I'd like to turn it back now to Charlie Fuchs and just ask him to share a couple of concluding remarks. Well, Barbara, thank you and all the panelists. It was a fantastic discussion and really provided so much insight in terms of how we continue to move grade science into the clinic and frankly how we learn more. About the tests in clinical trials that were actively doing
as part of our investigation, this is I mentioned is the third of our Yale engage cancer forms and I hope that our attendees enjoyed it and benefited from it. And as I mentioned, the work continues and we very much want this to be the beginning of the conversation and so hopefully what will what you’ll do and what we’ll do is engage each other in thinking through how we partner, how we work strategically together. To think of these, the ideas that are panels are brought
up an develop new initiatives,

so people should feel free to reach out to me or any of the panelists to think about.

These collaborations will be contacting you really appreciate your taking the time.

You know when I listen to discussions like this, I think it gives all of us hope and excitement about the years ahead of cancer investigation.

So let me just turn it back, to Barbara for some final thoughts.

You know, so I’ve been at Yale about 6 1/2 years and the conversation today.
Sort of reminds me of the excitement that I felt when I started going to seminars around here. I mean, there’s just unbelievable scale of work of this quality going on at this institution, and a lot of people thinking about how to make cancer treatment better. So thank you all for joining us today. Please stay in touch and I want to thank Susan and curtain, Katie and Mark and Megan Inch in for their wonderful presentation. Thank you very much.