I'm doctor Mary. I'm Lustberg. Thank you for joining in person and for those of you joining online. I'm pleased to introduce Doctor Louis Pushti as today’s ground round speaker. Doctor Pushki is professor of medicine. And Co director of the genomics, genetics and Epigenetics research program here at Yale. He received his medical degree from Semmelweis University of Medicine in Budapest and his Doctor of Philosophy degree from the
University of Oxford in England.

His research group has made important contributions to establish that estrogen receptor positive and negative breast cancers have fundamentally different molecular, clinical and epidemiological characteristics. He’s been a pioneer in evaluating gene expression profiling as a diagnostic technology to predict chemotherapy and endocrine therapy sensitivity. And as shown that different biological processes are involved in determining the prognosis and treatment response in different breast cancer subtype.
His group has also developed new bioinformatics tools to integrate information from across different data platforms in order to define the molecular pathways that are disturbed in individual cancers and could provide the basis. For individualized treatment strategies.

Doctor Pushki is a trusted colleague here at Yale and is a principal investigator of several clinical trials investigating new drugs, including immunotherapies for breast cancer.
and is among the top 1% most highly cited clinical investigators in medicine over the past 10 years.

Today he will speak on breast cancer, moving ever closer to cure for all.

Thank you so much Doctor Pushkar.

You can go ahead and start using this.

Thank you, Mary.

I’m so if you’re OK with you,

I will take this mask off because having a mask, my accent and my voice would be really serious.

Triple hit against me from the get go.

So I hope it’s OK with you.

It’s delighted to see that some people are in the auditorium because
00:02:47.334 --> 00:02:49.595 I actually forgot how to get here.

00:02:49.600 --> 00:02:52.444 So I really sympathize with those of you who are actually online with this.

00:02:52.444 --> 00:02:54.488 So I think I need to start with my disclosure slides.

00:02:58.480 --> 00:03:01.210 And then before I start my slides, I would actually like to make a confession to you and admit a weakness.

00:03:01.210 --> 00:03:03.289 It’s not chocolate,

00:03:03.290 --> 00:03:05.180 but I do feel like a child in a candy store surrounded by a lot of really delicious and very interesting scientific questions.

00:03:05.180 --> 00:03:07.207 So my weakness is that I have a really eclectic and very broad range of interests.

00:03:07.999 --> 00:03:10.367 It’s not chocolate,

00:03:10.367 --> 00:03:12.005 but I do feel like a child in a candy store surrounded by a lot of really delicious and very interesting scientific questions.

00:03:15.850 --> 00:03:18.271 So my weakness is that I have a really eclectic and very broad range of interests.
And don’t be scared,

I’m not going to talk about all of these questions,

but these are the type of questions that.

My group has been studying in the

past few years and I showed this here

for you to forgive me and understand

why I don’t show up to most of the.

Administrative meetings,

so these studying things like

cost effectiveness,

what’s the best cost effective

strategy in the new adjuvant

setting for for breast cancer,

why some preoperative chemotherapy

regimens produce high response rates
but very little improvement in survival.

and other regiments to the opposite

small improvements in response, large improvements in survival.

Why there is some women develop breast cancer 20-30 years before the median age?

Could we develop some sort of a tool to sum up all the genomic abnormalities?

From germline and somatic regions that would actually describe the capture

the totality of abnormalities in atom.

How comes that summer stragen receptor positive cancers recur as they are negative?

You know some ER positive cancers not fully ER positive,
00:04:22.050 --> 00:04:22.656 3040% positive.
NOTE Confidence: 0.88288054

00:04:22.656 --> 00:04:25.080 So what are the rest of those cells
NOTE Confidence: 0.88288054

00:04:25.142 --> 00:04:26.450 which are ER negative?
NOTE Confidence: 0.88288054

00:04:26.450 --> 00:04:28.385 What's their relationship to the
NOTE Confidence: 0.88288054

00:04:28.385 --> 00:04:29.546 ER positive cells?
NOTE Confidence: 0.88288054

00:04:29.550 --> 00:04:31.968 What novel therapeutic strategies one could
dig out from high dimensional genomic data.
NOTE Confidence: 0.88288054

00:04:31.968 --> 00:04:35.308 So what is the molecular phylogenetic
relationship between different
NOTE Confidence: 0.88288054

00:04:35.310 --> 00:04:37.920 metastatic lesions and the primary tumor?
NOTE Confidence: 0.88288054

00:04:37.920 --> 00:04:39.225 Is these different for synchronous
 NOTE Confidence: 0.88288054

00:04:39.225 --> 00:04:41.367 mats against asynchronous?
NOTE Confidence: 0.88288054

00:04:41.370 --> 00:04:43.205 That's you know why some Kansas are
NOTE Confidence: 0.88288054

00:04:43.205 --> 00:04:44.306 immune reaction immune poor was the
NOTE Confidence: 0.88288054

00:04:44.310 --> 00:04:46.515 immune reaction immune poor was the
NOTE Confidence: 0.88288054

00:04:46.515 --> 00:04:50.398 difference between the immune rich ER
NOTE Confidence: 0.88288054

00:04:50.398 --> 00:04:52.407 positive and PR negative terms is there
a difference in the microenvironment that's race influence this so really study all of these things and. You can look at the publications on them. So I'm only going to focus on a few which I think have a longer trajectory and contributed to the to this remarkable events that happened in the past 20 years that breast cancer survival and mortality decline, mortality decline by about 50%. I think this is primarily driven by new treatment strategies based on better understanding of the disease and the new
00:05:23.257 --> 00:05:25.159 classes of drugs that we developed.
NOTE Confidence: 0.88220373
00:05:25.160 --> 00:05:27.338 And I think the journey is
NOTE Confidence: 0.88220373
00:05:27.338 --> 00:05:29.360 just just about to begin.
NOTE Confidence: 0.88220373
00:05:29.360 --> 00:05:32.310 So how new treatment strategies
NOTE Confidence: 0.88220373
00:05:32.310 --> 00:05:34.080 could influence outcome?
NOTE Confidence: 0.88220373
00:05:34.080 --> 00:05:36.480 So in the early 2000s,
NOTE Confidence: 0.88220373
00:05:36.480 --> 00:05:38.461 I was in the right place at
NOTE Confidence: 0.88220373
00:05:38.461 --> 00:05:40.390 the right time at MD Anderson,
NOTE Confidence: 0.88220373
00:05:40.390 --> 00:05:42.045 we were interested to explore
NOTE Confidence: 0.88220373
00:05:42.045 --> 00:05:43.038 period preoperative chemotherapy
NOTE Confidence: 0.88220373
00:05:43.038 --> 00:05:44.821 for women who actually had operable
NOTE Confidence: 0.88220373
00:05:44.821 --> 00:05:46.423 disease and we assumed that they
NOTE Confidence: 0.88220373
00:05:46.472 --> 00:05:48.208 would end up with a better cosmetic
NOTE Confidence: 0.88220373
00:05:48.208 --> 00:05:49.288 outcome as smaller disease.
NOTE Confidence: 0.88220373
00:05:49.288 --> 00:05:50.600 And at that time,
NOTE Confidence: 0.88220373
00:05:50.600 --> 00:05:52.346 it was a pretty controversial idea
and there was really no good way to either define the response.

How do you measure the efficacy of these preoperative regimens?

Do you measure it by response? On imaging or we measured by the extent of residual disease.

So we proposed the definition which eventually become the standard of care definition that you have no residual invasive cancer in the breast or lymph nodes and that’s kind of the best outcome that you could get.

So with this definition it pretty quickly become available become
obvious that individuals accomplish this complete pathological response.
It really well regardless of what type of breast cancer they had,
they are positive or negative. Those who had residual disease didn’t do so.
And this immediately defines you what you actually want to accomplish in the clinic, right?
You want to put more patients into these pathologic CR category and you want to hurt harm.
Do you wanna help those who are in the residual disease group?
So we did that in the past 20 years.
So you see the evolution of the chemotherapy.

Regiments, in 2008 when we published this paper on the survival curves, the best chemotherapy was Taxol anthracyclines. It produced about a 30-35% complete response rate, in particular negative disease and now we have doubled that. So now we actually accomplish about a 63% complete response rate by adding an immunotherapy drug. And you also learn that adding other chemotherapy agents like carboplatin
00:07:12.727 --> 00:07:14.827 improves the pathologic CR rates.
NOTE Confidence: 0.88220373
00:07:14.830 --> 00:07:16.370 We have regiments that don’t
NOTE Confidence: 0.88220373
00:07:16.370 --> 00:07:17.602 include the anthracyclines that
NOTE Confidence: 0.88220373
00:07:17.602 --> 00:07:19.286 some of my colleagues think that.
NOTE Confidence: 0.88220373
00:07:19.290 --> 00:07:21.936 Is the chemical incarnation of the devil.
NOTE Confidence: 0.88220373
00:07:21.940 --> 00:07:24.894 Also there are even single agent therapies,
NOTE Confidence: 0.88220373
00:07:24.900 --> 00:07:27.170 targeted therapies like PARP inhibitors
NOTE Confidence: 0.88220373
00:07:27.170 --> 00:07:28.986 that produce pretty respectable
NOTE Confidence: 0.88220373
00:07:28.986 --> 00:07:30.660 pathology company eradication of
NOTE Confidence: 0.88220373
00:07:30.660 --> 00:07:33.104 the cancer before surgery in in
NOTE Confidence: 0.88220373
00:07:33.104 --> 00:07:34.460 germline Brockhampton patients.
NOTE Confidence: 0.88220373
00:07:34.460 --> 00:07:36.868 But we also made him really important
NOTE Confidence: 0.88220373
00:07:36.868 --> 00:07:38.964 improvements for in the life of
NOTE Confidence: 0.88220373
00:07:38.964 --> 00:07:40.624 those who have residual disease.
NOTE Confidence: 0.88220373
00:07:40.630 --> 00:07:42.634 So those are three randomized clinical
NOTE Confidence: 0.88220373
00:07:42.634 --> 00:07:44.321 trials that established the value
00:07:44.321 --> 00:07:45.791 of giving capsidae in chemotherapy
00:07:45.791 --> 00:07:47.778 for those and the residual disease
00:07:47.778 --> 00:07:49.298 with triple negative cancer.
00:07:49.300 --> 00:07:51.430 And the Olympia study showed that
00:07:51.430 --> 00:07:53.026 that whole party improves the
00:07:53.026 --> 00:07:54.571 response within a similar population
00:07:54.571 --> 00:07:56.329 if the average germline Broca's.
00:07:56.330 --> 00:08:00.193 And the Catherine study did the
00:08:00.193 --> 00:08:02.146 Godzilla for her to post the disease.
00:08:02.150 --> 00:08:03.860 But I want to spend a few minutes on
00:08:03.860 --> 00:08:06.158 how do we get there, in particular,
00:08:06.158 --> 00:08:10.662 how we actually came about to establish
00:08:10.662 --> 00:08:13.877 the value of immunotherapy in.
00:08:13.880 --> 00:08:16.036 In breast cancer. So the roots of
This idea that immunotherapy might work in breast cancer has been long rooted in preclinical studies. But also in the early 2000s a number of groups reported that even in patients who only receive surgery, the amount of immune cells in the tumor microenvironment is hugely prognostic. So this is what the first half of this slide shows you survival curves for patients who did not receive any other treatment than surgery, for patients who did not receive any other treatment than surgery, they were stratified into three groups. Little high immune presence, intermediate in presence or low immune presence and you see that...
that the immune cells have a massive prognostic value in all three categories of breast cancer subtypes including the ER positive patients. And what we used in this particular study was gene signature to define the immune richness. They’re in the same time German investigators showed that the presence of immune cells also predicts the probability of complete pathological response. But this slide shows you 32 important things. One is that in the red circles you see the pathologic computer response.
00:09:18.814 --> 00:09:22.538 Rates by tumor infiltrating into side.
NOTE Confidence: 0.798355488695652
00:09:22.540 --> 00:09:22.893 Presence.
NOTE Confidence: 0.798355488695652
00:09:22.893 --> 00:09:25.011 So they grouped the cases into
NOTE Confidence: 0.798355488695652
00:09:25.011 --> 00:09:26.430 No lymphocytes, some lymphocytes,
NOTE Confidence: 0.798355488695652
00:09:26.430 --> 00:09:27.850 Lymphocyte predominant and you
NOTE Confidence: 0.798355488695652
00:09:27.850 --> 00:09:29.810 See that the pathologic CR rates
NOTE Confidence: 0.798355488695652
00:09:29.810 --> 00:09:31.504 These numbers in the in the little
NOTE Confidence: 0.798355488695652
00:09:31.504 --> 00:09:33.251 Blood red circles increase as you
NOTE Confidence: 0.798355488695652
00:09:33.251 --> 00:09:34.706 Have more and more lymphocytes.
NOTE Confidence: 0.798355488695652
00:09:34.710 --> 00:09:37.176 So for example in the blue,
NOTE Confidence: 0.798355488695652
00:09:37.180 --> 00:09:39.940 So the square or highlighted
NOTE Confidence: 0.798355488695652
00:09:39.940 --> 00:09:42.700 Area and ER positive disease,
NOTE Confidence: 0.798355488695652
00:09:42.700 --> 00:09:43.660 We know lymphocytes,
NOTE Confidence: 0.798355488695652
00:09:43.660 --> 00:09:45.477 It’s a very small 6% PCR.
NOTE Confidence: 0.798355488695652
00:09:45.477 --> 00:09:46.996 If you have a lot of lymphocytes,
NOTE Confidence: 0.798355488695652
00:09:47.000 --> 00:09:49.922 It goes up to a respectable 23% and you see
this same trend across all the subtypes.

So of course these observations lead to a lot of other questions then.

So why some breast cancers are immune, originalists don’t is the immune microenvironment differ between the primary system and the maths, it’s a different by ER subtype or by race? And ultimately the the most important question is this a causal relationship or immune cell presence is actually responsible for the good outcome or it’s just an association that reflects some other underlying biology. So when these papers were published,
you couldn't really test this in people, there were no chemotherapy drugs.

But now we have and we actually have the answer to most of these and I put there some of the publications that address these issues.

So I want to share with you some results which I think really informed a lot of my thinking about the role of immune system in breast cancer.

A few years ago Anton Sofronoff downloaded all the CG data or AC DNA copy number, mutation data, germline snips and asked this question.
So what drives the immune infiltration and breast cancers? We looked at Chrono Heterogeneity, mutation load, new antigen load, copy number variations, germline snips, single gene somatic mutations, pathway level abnormalities, which of these is associated with high immune presence, whether you think the results showed? So. Gosh. So the results are actually quite counterintuitive. So what this shows you is a correlation.
00:11:27.742 --> 00:11:29.446 matrix of about 12 immune gene
NOTE Confidence: 0.798638677142857
00:11:29.446 --> 00:11:31.472 signatures that we use to define the
NOTE Confidence: 0.798638677142857
00:11:31.472 --> 00:11:33.474 immune presence or absence or in your
NOTE Confidence: 0.798638677142857
00:11:33.474 --> 00:11:35.626 richness and about 6 genomic features.
NOTE Confidence: 0.798638677142857
00:11:35.626 --> 00:11:38.519 So the darker brown shows a higher
NOTE Confidence: 0.798638677142857
00:11:38.519 --> 00:11:40.784 correlation value and the darker
NOTE Confidence: 0.798638677142857
00:11:40.784 --> 00:11:43.570 blue shows a negative correlation.
NOTE Confidence: 0.798638677142857
00:11:43.570 --> 00:11:45.292 And you see right away that
NOTE Confidence: 0.798638677142857
00:11:45.292 --> 00:11:46.861 the immune gene signatures are
NOTE Confidence: 0.798638677142857
00:11:46.861 --> 00:11:48.309 highly correlated one another,
NOTE Confidence: 0.798638677142857
00:11:48.310 --> 00:11:49.375 whereas they are not correlated
NOTE Confidence: 0.798638677142857
00:11:49.375 --> 00:11:50.728 very closely at all. In fact,
NOTE Confidence: 0.798638677142857
00:11:50.728 --> 00:11:52.720 they are anti correlated with many of the.
NOTE Confidence: 0.798638677142857
00:11:52.720 --> 00:11:53.404 Economic features.
NOTE Confidence: 0.798638677142857
00:11:53.404 --> 00:11:55.798 So and you see this across the
NOTE Confidence: 0.798638677142857
00:11:55.798 --> 00:11:57.830 board in all the three subtypes.
So in primary breast cancer greater chromo heterogeneity and higher mutation and neoantigen loads are associated with lower immune infiltration. So there was such a weird finding that we actually teamed up with the A colleague from Germany, Thomas Cohn to really confirm this in an independent data set and we find the same result. So why is this interesting? Because even though we found no share genomic alterations that drive the immune infiltration in breast cancer, we really find a strong supportive.
evidence that there is an active immune editing in early stage disease,
right.
So a lot of immune cells in actually called remove chromo heterogeneity and that’s why you have a chromoly simple tumor and actually a lower your antigen load because the cancer cells with the high neoantigen load are removed by the immune system.
So that’s really attractive.
Hypothesis and it makes testable predictions.
So one prediction is that even tumor cells sort of undergo medical transformation.
Some of it could be eliminated by the immune system.
So if that’s really true, then actually immunotherapy should work as chemoprevention. Of course, it’s too toxic to do that, but the concept is important. So we’re going to test this in an ongoing large event trial that uses symbolism for a year to see whether it alters contralateral breast cancer events and also whether it alters breast density. Which is sort of a somewhat validated risk predictor. But the most important consequence is this that when we actually diagnose these cancers,
there may be a quasi equilibrium fight between the immune system and the cancer. So when there are a lot of immune cells, it's kind of indicate that the immune system is having almost upper hand and that's why it actually is associated with better prognosis. But at that stage you might actually help tip the balance towards the immune system by chemotherapy or by immune checkpoint inhibitors and then. Do not have the drugs to test this. And we actually launched 4 studies to address these questions and three of them have results, and I'll show that to you.
But the third prediction is also interesting, right?

So if you really follow this logic, then the metastatic disease should really arrive through an immune escape.

We did a series of studies to compare primary exams and maths, and it’s among the first groups to show that actually metastatic lesions in breast cancer are profoundly immunocompromised. And we also looked at whether there is subtle variations by sight.

So now these are all sort of relatively valid accepted principles.
I thought I showed this to you, especially for those of you who are younger investigators. So there are risks of coming up with an idea too early or too late. This particular idea came on a little bit too early. In 2012, about a month of Tiki came here. I approached Merck to do 2 large studies in the curative setting. What was the neoadjuvant trial to see whether we could actually push the PCR? It’s up based on the associations that I showed you to test the causality. The other one was an adjuvant study.
giving people liberalism out and eradicate.

Micromedex and this is what they said, sorry you’re unable to avoid the drug and the monetary support at this time due to unclear regularly path forward.

But it was three years later they actually realized that there is a path forward and they actually run both of these studies or or agree to do it and they to their credit they actually invited me back to their steering committee of the new adjuvant trial and I lead the adjuvant trial.

So what do these studies show it? This is just the selection that is
representative of the findings from the neoadjuvant immunotherapy trials. And they were lounged in triple negative disease because of the really strong association of immune cells with pathologic CR or strong association with prognosis. So all these studies took place in that space except one, the ice spy all talk to you a little bit more about it. So what this study shows is that the computer response rates improved. Didn’t have as much as we thought.
So the largest study keynote 5 to 2, the Merck study showed improvement about 7 percent, 56 to 63. Really underwhelming because chemotherapy trials could do double digit improvements. Yet the chemo studies actually didn’t really improve the event dramatically. Oftentimes it didn’t deal with it all to a significant extent. But keynote 522 did. You see the same in an even smaller study, paranormal. They’re also showed a 9% even PCR rate. Not even significant,
but the event free survival was significant.

Important finding in this sort of observation from these studies is that in metastatic disease, again parallelism have improved the outcome when combined with chemotherapy. But this was only seen in the pediatric and positive patients whereas in the early stage setting you don’t need to have Pedalyte and one. So that confuses a lot of people. But I think there is a really simple and elegant explanation and it comes from the slide that I showed you previously.
from the fact that the metastatic lesions are immunocompromised or really immunosuppressed immune attenuated so.

And the only stage setting I think a small amount of immune presence that you could miss with the biopsy and they actually miss it oftentimes with biopsy. So even a few period like in one positive cells that are intermixed with the micro environment and missed the initial biopsy could be enough to actually ignite an immune response and the same.
way chemotherapy ignites sort of like one expression in the more massive scale, but you don’t see the same thing in the metastatic setting. So the other question was this really? This thing observation that why small improvements in Pathologic CR really lead to large improvements in survival whereas in other setting it doesn’t happen. So that brings me to another sort of debate that used to rage and the breast cancer community and we spent a lot of time on it. It’s really prompted by the initial new adjuvant trials and shovel power to show improvement in PCR.
but was woefully underpowered and included all subtypes to really show improvement in survival.

So this matter analysis by the FDA showed very little in fact no relationships at all between improvement in PCR and survival.

They confused a lot of people, but it would have to fly against the totally common sense.

Observations, Taxol improved pathologic, sciarid improved survival receptive improved Pathologic CR, it improves survival.

Platinum improved Pathologic CR
it’s and now we know that it improves survival as well. And of course the immune checkpoint inhibitors improved pathologic security improve survival. But nevertheless it’s really true that at the individual trial level the relationship between the PCR change improvement and the improvement in PFS is hugely variable. So that’s the next question to study why and I actually have a good explanation for you. And I think it’s very elegant and simple. But to understand that you need to familiarize yourself with this.
The concept of a continuous metric of outcome or pathological response. So again in 2007 we developed this metric called residual cancer burden to capture the pathological residual disease as a continuous variable. We did that because continuous variables are more powerful to identify genes that would be associated with outcome or not. Eventually, it took sort of traction in the form of categories, so you can use this continuous score to create bins of 0 being complete response. Another bin.
00:19:17.898 --> 00:19:19.493 That’s the minimal residual disease
NOTE Confidence: 0.866753938666667
00:19:19.493 --> 00:19:21.578 or RCB 1 moderate amount or CB2
NOTE Confidence: 0.866753938666667
00:19:21.578 --> 00:19:23.360 and a large amount of RCB 3.
NOTE Confidence: 0.866753938666667
00:19:23.360 --> 00:19:25.720 But the truth is that this is really
NOTE Confidence: 0.866753938666667
00:19:25.720 --> 00:19:27.161 a continuous scroll and that’s
NOTE Confidence: 0.866753938666667
00:19:27.161 --> 00:19:28.476 why we did it so.
NOTE Confidence: 0.866753938666667
00:19:28.480 --> 00:19:31.168 Be teamed up the deal I spoke
NOTE Confidence: 0.866753938666667
00:19:31.168 --> 00:19:32.320 to investigators because
NOTE Confidence: 0.683619764
00:19:32.395 --> 00:19:34.530 this continuous sort of score,
NOTE Confidence: 0.683619764
00:19:34.530 --> 00:19:36.175 I thought actually could reveal
NOTE Confidence: 0.683619764
00:19:36.175 --> 00:19:37.491 some really interesting things
NOTE Confidence: 0.683619764
00:19:37.491 --> 00:19:39.078 about how different drugs work.
NOTE Confidence: 0.683619764
00:19:39.080 --> 00:19:41.969 So what you see here is actually a pretty
NOTE Confidence: 0.683619764
00:19:41.969 --> 00:19:45.299 cool picture of the continuous RCB scores in
NOTE Confidence: 0.683619764
00:19:45.299 --> 00:19:48.097 seven different arms of the eye spy study.
NOTE Confidence: 0.683619764
00:19:48.100 --> 00:19:49.745 So the eye spy is randomized trials,
the control arm is always staxel ACC,

and but you see here is the RCB values from zero to 50 is complete response.

Five is expensive.

Single disease.

This kind of shows you the the the prevalence of the density or the frequency with which you encounter a particular RCB value in the trial arm.

So the black is the control and the dotted lines are various experimental drugs.

I just want to look at you the two panels which are labeled so I don’t think I can use a A.

Sort of a pointer,
but you probably see there
NOTE Confidence: 0.683619764
that the bottom panel,
NOTE Confidence: 0.683619764
which is regimen 7,
NOTE Confidence: 0.683619764
you have a large improvement in PCR rates,
NOTE Confidence: 0.683619764
right, because the the initial
NOTE Confidence: 0.683619764
zero values are much higher.
NOTE Confidence: 0.683619764
That’s where the curves start.
NOTE Confidence: 0.683619764
But you also see a massive shift towards
NOTE Confidence: 0.683619764
the smaller values across the board.
NOTE Confidence: 0.683619764
If you look at the Regiment 3 on the
NOTE Confidence: 0.683619764
top instead of right hand corner,
NOTE Confidence: 0.683619764
then you see that that regimen
NOTE Confidence: 0.683619764
also improves PCR rates.
NOTE Confidence: 0.683619764
But it does it by moving the RCB 1,
NOTE Confidence: 0.683619764
the little residual disease group,
NOTE Confidence: 0.683619764
into the PCR company response.
And that is very unlikely to affect survival like it doesn’t. But this particular regimen didn’t affect at all the higher residual cancer. So we thought that actually measuring the distribution of the differences in residual cancer burden scores could capture the efficacy of a regimen. And we developed a new statistical tool that you can find in this paper and you can even play with it if you have a breast cancer on this open website, we call it treatment efficacy score and it basically compares the distribution of RCB scores.
Cross through trial arms in that particular metric actually really correlates quite well with event free survival which is what you see. There’s a significant difference. Is that all significant improvement in this test score then you don’t have significant improvement in event free survival. So we’re going to validate this within with the other groups. So we’re not move to this other question that these studies show up, right. So pembrolizumab is expensive and 15% of the patients have severe toxicity,
He entered into this race to find predictive markers that define the patients who need pembrolizumab and this is a slide from a group in Germany civil libel. And one of my former lab members Thomas Kuhn, who leads their translational research arm. And what they show in this randomized immunotherapy versus chemotherapy alone ARM study that there are a number of molecular variables that predict response to any if you have them like high commutation burden or a high Energy and expression or high P like in
one expression or high till comes you

have higher PCR rate with chemotherapy,

chemotherapy but also with

chemotherapy plus immunotherapy.

But the improvement by immunotherapy

happens in both groups,

the remediation low and high,

the PD low and high or the field

So these are these one of these

metrics are selective to identify

who actually needed the panel,

but we have an idea who actually

might benefit from Pedro.

So we teamed up with the investigators.

On the build who previously suggested
that MH subclass 2 expression in tumor cells might actually identify a group, the group of patients who really need it Pembroke. So I need to see class to is is mostly expressed in immune cells and participates in antigen presentation, but it can be induced to be expressed in cancer cells and epithelial cells by interferon gamma, for example, so. Have you run this immunity chemistry, a simple immunity chemistry for emission classical expression on cancer as opposed to the immune cells. And we actually confirmed that what
Justin Balko originally reported that the cancers which were positive for MHC Class 2 expression actually had a higher pathologic CR rate when Pembroke was added in the ice spy study. But the pathologic CR it was the same whether they were MHC Class 2 high or low if they only got chemotherapy and so. They really strong interaction, marker treatment interaction in that study and parallel with this completely independent. Another set of former lab member of mine, Jean-paul Bianchini showed the same thing in their new adjuvant.
trial without the salesman.

You know, I highlighted for you the interaction between Italy, the expression on epithelial cells that actually predicted higher odds ratio for PCR.

Vidot is always the map but didn’t have any sort of significant other ratio with chemotherapy alone, but the same.

Study our immune cells didn’t carry this. So it’s a really cool project there and we just got funding from the NCI to kind of test this and validate this in a larger trial them S 1418 that I.
00:24:30.710 --> 00:24:33.010 I mentioned to you earlier.
NOTE Confidence: 0.626329596666667
00:24:33.010 --> 00:24:33.506 But again,
NOTE Confidence: 0.626329596666667
00:24:33.506 --> 00:24:35.242 so this study is the fascinating thing
NOTE Confidence: 0.626329596666667
00:24:35.242 --> 00:24:36.962 about science is that every advance
NOTE Confidence: 0.626329596666667
00:24:36.962 --> 00:24:38.382 actually throws up new questions,
NOTE Confidence: 0.626329596666667
00:24:38.390 --> 00:24:40.574 even more interesting questions.
NOTE Confidence: 0.626329596666667
00:24:40.574 --> 00:24:44.160 So one question is why some cancers
NOTE Confidence: 0.626329596666667
00:24:44.160 --> 00:24:45.659 are important in reach, right?
NOTE Confidence: 0.626329596666667
00:24:45.659 --> 00:24:47.213 A lot of people are struggling
NOTE Confidence: 0.626329596666667
00:24:47.213 --> 00:24:47.990 to find answers,
NOTE Confidence: 0.626329596666667
00:24:47.990 --> 00:24:50.710 how you make a cold against the heart.
NOTE Confidence: 0.626329596666667
00:24:50.710 --> 00:24:52.243 But we thought we ask something a
NOTE Confidence: 0.626329596666667
00:24:52.243 --> 00:24:53.712 little bit more original and maybe
NOTE Confidence: 0.626329596666667
00:24:53.712 --> 00:24:55.810 something that that could be easier to crack.
NOTE Confidence: 0.626329596666667
00:24:55.810 --> 00:24:57.250 And that’s the question,
NOTE Confidence: 0.626329596666667
00:24:57.250 --> 00:24:59.050 why doesn’t all immune high

48
cancers actually accomplished PCR? Why is the PCR only 63%? And 100 or 90 that’s a project that Kim actually came women led and we compared the immune reach triple negative disease that had the PCR versus those that did not. And we find really pretty interesting stuff that I think could lead us to some leads about what combination therapies, immunotherapies could really be make embolism and more effective. So just to summarize let’s we found that the teacher have better if
one teacher beat is high in the immune microenvironment even if you are in reach. You don’t accomplish PCI and a lot of innate immunity markers are also associated with it. The innate immunity markers actually are macrophage and K markers and when you look at the cytokine milieu then you really see this very strikingly so cancers it raises your disease. The dominant cytokines are actually cytokines which are involved in chemotaxis and activation of neutrophils and macrophages. So we hypothesized they’re blocking. Some of those would actually improve
00:26:01.190 --> 00:26:05.120 the outcome or the efficacy. Of.
00:26:05.120 --> 00:26:06.784 You actually went pembrolizumab.
00:26:06.784 --> 00:26:09.280 So interestingly I just put that asterisk for you to to that.
00:26:09.347 --> 00:26:11.135 It’s so beautiful because it congruent.
00:26:11.140 --> 00:26:13.078 So we find that a lot of these very same cytokines that we see highly present in immune rich non responding TNBC at the very same chemokines and silicones that we find in the metastatic microenvironment.
00:26:13.080 --> 00:26:15.393 right in that paper that showed that the metastatic microenvironment is more immuno attenuated.
00:26:15.393 --> 00:26:17.491 And instead of finish these sort of
00:26:17.491 --> 00:26:19.726 present in immune rich non responding TNBC at the very same chemokines and silicones that we find in the microenvironment metastatic disease right in that paper that showed that the metastatic microenvironment is more immuno attenuated.
00:26:19.726 --> 00:26:22.120 And instead of finish these sort of
series of questions and immunotherapy off.

So if immunotherapy works beautifully entrepreneur disease,
could it actually work in a subset of ER positive cancers.

And we think that it will work because we noticed in the eye spy trial data that in three arms that included immunotherapy including the door volume up, Olaparib arm, the Iliad, the Penrose Metaxa arm and the pembrolizumab and it’s all like receptor antagonist. Arm in all of these three arms independently we saw that among the ER positive here we call them HR hormone receptor positive cancers.
There is a group that is characterized by routinely reported sort of molecular feature, the ultra high mammaprint status. So all of these patients had to have high mammaprint result. High MAMMAPRINT defines patient superficially benefit from chemotherapy but within that high mountain group you can devise an agent, they actually introduce their system. The device to group smaller print high high and some Withrow high. So the small print we throw higher MP two group is the subset among the ER positive patients who benefited.
and it’s really, really elegant. You can’t see that right. So the HR positive MP1, there’s no difference whether you get chemo plus durva, but if you are MP two then Nirvana improves your PCR. It’s same for pembrolizumab with the other two arms. And what’s even nicer when you look at the molecular features of these empty two patients, their ER signaling and. Yeah, sort of the gene signatures that typically
00:28:04.850 --> 00:28:06.699 associated with endocrine sensitivity,

00:28:06.700 --> 00:28:07.321 this is low.

00:28:07.321 --> 00:28:08.563 So that’s the group let’s see

00:28:08.563 --> 00:28:10.376 are positive but least likely to

00:28:10.376 --> 00:28:11.620 benefit from endocrine treatment.

00:28:11.620 --> 00:28:13.650 They have sort of a higher proliferation

00:28:13.650 --> 00:28:15.139 signature which also makes sense.

00:28:15.140 --> 00:28:17.030 So they are more sensitive to chemotherapy

00:28:17.030 --> 00:28:18.897 and we also saw this in the the,

00:28:18.900 --> 00:28:20.690 the chemotherapy arms and but

00:28:20.690 --> 00:28:22.958 we didn’t really see a major

00:28:22.958 --> 00:28:24.988 difference in the immune micro

00:28:24.988 --> 00:28:27.100 in immune signature genes.

00:28:27.100 --> 00:28:30.594 So again we hope to launch the prospective

00:28:30.594 --> 00:28:32.436 study that would validate this concept.
With the routinely available essay we could actually identify a group that will benefit from the same way as triple negative disease benefited from including immune checkpoint therapy. So just to summarize these clinical partially the paradigm shift that happened in the past sort of 20 years is that the best way to treat most stage two and stage three triple negative patients is new adjuvant chemotherapy and the best PCR rates are accomplished about two third of the patients having a competent navigation of the cancer, the same happened in her two
positive disease.

Don’t talk about this because it’s really predated at least by 1015 years, the immunotherapy revolution and there are a lot of really interesting studies that will push the survival even further among those who have residual disease. So there are new studies that are launched in that space that I kind of highlighted for you. So what’s next, right. So what’s going to be the next paradigm shift in the next 10 years?
And I think this is really.

I see two really potentially very high impact fields which we could improve again survival within the next 5 to 10 years and which is. So wait a second.

Yeah. So what is coming up with this concept that could we detect molecular relapse in solid tumors the same way as we detect molecular relapse in leukemia. If you see that with PCR that your genomic abnormalities returned, then a second round of treatment at that point would actually cure some people from leukemia. So could the same paradigm apply to
sometimes it didn’t really have
good ways to catch this and we didn’t
really have good effective drugs
either 5610 years ago to test this,
but now we have most molecular.
Essays that can pretty reliably
identify and the SEC DNA is
particularly tumor informed C DNA.
So if you have a high C DNA level
that’s starting to rise while you
are in the surveillance of follow
up stage of the initial curative
therapy as the city then rises,
unfortunately it’s almost sure bad that you
will have a recurrence clinical recurrence
within the next seven or eight months.

So could we intervene at that point when people are still sort of micrometastatic but the micrometastasis is raising its ugly head?

So that’s an idea of a second line. I look in therapy and we actually lead a study. We have a study in that space that that’s exactly this idea in your positive patients who are receiving endocrine therapy but start to have a rising CDN, they randomized the full Western public cycling and. And we’ll just continue with their standard of care treatment and get treatment.
when they become clinically symptomatic.

So the other potentially paradigm shifting idea is really that they could cure some metastatic disease.

So you have metastatic disease kind of the current dogma is that you will die from it. It may take many, many years, but ultimately people die.

I’m not sure that this actually has to happen like this. So what happened in the past five, six years is that you really understood much more clearly that there are multiple. Different types of meds,
not just some medicine.

Disease doesn’t exist.

There’s a homogeneous entity,

just like the breast cancer doesn’t exist to looking. It doesn’t exist.

It’s a useful concept.

But practically really these are all very there are many,

many different types of leukemias that require different approaches and treatments,

different types of breast cancers.

And the same way like metastatic disease is also heterogeneous.

So the novel stage for disease is unique because it never received any prior therapy.

That’s obviously very different
00:31:55.032 --> 00:31:56.424 from somebody relapsing and having a metastatic disease.
00:31:56.424 --> 00:31:58.150 After they went through all the chemotherapies was embolism and whatnot.
00:32:00.482 --> 00:32:01.480 So curing those folks with existing therapies is a long shot,
00:32:01.480 --> 00:32:04.396 the chemotherapies was embolism and whatnot.
00:32:04.400 --> 00:32:05.965 So curing those folks with existing therapies is a long shot,
00:32:05.965 --> 00:32:07.880 existing therapies is a long shot,
00:32:07.880 --> 00:32:09.518 but curing those folks who never had any therapy with the combination of drugs is probably not such a long shot.
00:32:09.518 --> 00:32:10.961 any therapy with the combination of drugs is probably not such a long shot.
00:32:10.961 --> 00:32:12.840 drugs is probably not such a long shot.
00:32:12.840 --> 00:32:15.038 And there are many case reports and anecdotal cases of metastatic patients,
particularly with her two positive disease because her two positive disease had the best drugs initially. The her two targeted drugs, but now we have good drugs for triplet disease as well. And also for your poster disease, so this paradigm that really kind of put into the mind of many practicing physicians that some her two positive cancer can be cured. I think it’s kind of increasingly applicable to the other subtypes as well. So we hope to do a study that would actually focus on covad especial group of her of metastatic patients,
they de Novo newly diagnosed metastatic patients particularly with oligo metastatic disease,
so that we could really get rid of all the known homicides and what’s left.
Is micromass, but we can deal with micro Mets. That’s the success story that I showed you.
That’s how adjuvant therapy improves survival after removing the the primary breast cancer in the lymph nodes,
the systemic therapy. Washes and and and kills them at the Micromax.
So I think this better than probably
00:33:15.129 --> 00:33:16.828 will hold up in stage four disease
NOTE Confidence: 0.774022176190476
00:33:16.828 --> 00:33:18.274 and the vision is very simple.
NOTE Confidence: 0.774022176190476
00:33:18.280 --> 00:33:20.305 So in five or ten years you don’t
NOTE Confidence: 0.774022176190476
00:33:20.305 --> 00:33:22.507 call these patients the oligo metastatic
NOTE Confidence: 0.774022176190476
00:33:22.510 --> 00:33:23.900 stage four patients stage four,
NOTE Confidence: 0.774022176190476
00:33:23.900 --> 00:33:26.228 but you call them stage 3C.
NOTE Confidence: 0.774022176190476
00:33:26.230 --> 00:33:28.150 Because they are deep, sorry.
NOTE Confidence: 0.774022176190476
00:33:28.150 --> 00:33:30.880 Because then they will be curable.
NOTE Confidence: 0.774022176190476
00:33:30.880 --> 00:33:33.085 So I’m going to move on to some other
NOTE Confidence: 0.774022176190476
00:33:33.085 --> 00:33:35.149 projects that I also find amazing and I
NOTE Confidence: 0.774022176190476
00:33:35.149 --> 00:33:37.237 just wanna share you some of the results.
NOTE Confidence: 0.774022176190476
00:33:37.240 --> 00:33:39.382 So why do some women develop breast
NOTE Confidence: 0.774022176190476
00:33:39.382 --> 00:33:41.218 cancer 20-30 years earlier than the
NOTE Confidence: 0.774022176190476
00:33:41.218 --> 00:33:43.206 average or median age even in the
NOTE Confidence: 0.774022176190476
00:33:43.264 --> 00:33:45.139 absence of any germline mutation?
NOTE Confidence: 0.774022176190476
00:33:45.140 --> 00:33:46.810 Actually that’s the majority of
young women with breast cancer.

It’s only a minority who has broken mutations rather identified mutations.

So we had two ideas.

One was that each is the strongest non genetic risk factor for breast cancer.

So could you actually sort of hypothesize that young women?

Could be breast cancer actually experience an accelerated epigenetic age of their breast.

So this was an idea that Erin Hofstatter, our former colleague picked up and we did a series of publications that actually suggests that this
00:34:14.196 --> 00:34:15.195 is indeed happening.

NOTE Confidence: 0.774022176190476

00:34:15.200 --> 00:34:17.468 So it shows you this insert from

NOTE Confidence: 0.774022176190476

00:34:17.468 --> 00:34:19.209 the the clinical epigenetics paper

NOTE Confidence: 0.774022176190476

00:34:19.209 --> 00:34:21.659 in 2018 shows this the most sort

NOTE Confidence: 0.774022176190476

00:34:21.659 --> 00:34:23.340 of simply and clearly.

NOTE Confidence: 0.774022176190476

00:34:23.340 --> 00:34:25.461 So what you should what you see

NOTE Confidence: 0.774022176190476

00:34:25.461 --> 00:34:27.594 there is each acceleration in the

NOTE Confidence: 0.774022176190476

00:34:27.594 --> 00:34:29.898 normal breast tissue of women who

NOTE Confidence: 0.774022176190476

00:34:29.898 --> 00:34:32.237 had breast cancer later and the.

NOTE Confidence: 0.774022176190476

00:34:32.240 --> 00:34:33.605 Epigenetic age acceleration of people

NOTE Confidence: 0.774022176190476

00:34:33.605 --> 00:34:34.970 who never develop breast cancer.

NOTE Confidence: 0.774022176190476

00:34:34.970 --> 00:34:37.282 So we did this with the Susan Comment

NOTE Confidence: 0.774022176190476

00:34:37.282 --> 00:34:39.805 Tissue Bank and with some tissues from here.

NOTE Confidence: 0.774022176190476

00:34:39.810 --> 00:34:42.330 So you see that there is a

NOTE Confidence: 0.774022176190476

00:34:42.330 --> 00:34:43.050 significant acceleration.

NOTE Confidence: 0.774022176190476

00:34:43.050 --> 00:34:44.942 So epigenetically speaking based
on the methylation signature,

the breast normal breast tissues of

woman who subsequently developed breast

cancer is older than their chronological age.

And we don’t see this to such

extent in the control patients.

And then and then we had some follow

up patients which really kind of

papers that explained that it’s mostly.

Polycom related genes whose

methylation pattern is associated

with this age acceleration,

and this last paper on the review in

science advances shows that actually every

cell proliferation adds a little bit of

69
epigenetic aging to the tissues. And there is a share of epigenetic signature between cancers and normal cells and it relates to aging and it relates to ultimately cell divisions. But it’s probably not the full story though. So what’s the rest of the story? So family history is a predictive risk factor even in the absence of any detectable hyper reference gene mutations, right? So something you inherited increases your risk, even if it’s you can’t see it so. Polygenic risk scores that use individual snips that are individually associated with risk to a very small extent,
00:35:51.800 --> 00:35:53.284 sum them up and you've made them

00:35:53.284 --> 00:35:54.799 by the risk that they confer.

00:35:54.800 --> 00:35:55.960 That's a polygenic risk score.

00:35:56.342 --> 00:35:59.016 However, even the best ones today using several

00:35:59.016 --> 00:36:00.932 100 risks polygenic risk and have

00:36:00.932 --> 00:36:03.000 a lot of missing heredity in them.

00:36:03.000 --> 00:36:05.296 So they don't explain this complete story.

00:36:05.300 --> 00:36:11.209 So we have this other idea that could

00:36:11.209 --> 00:36:13.029 germline variants and cancer relevant

00:36:13.030 --> 00:36:14.326 Because they are not recurrent.

00:36:14.330 --> 00:36:16.286 Missed them in indigenous studies,
because they start out finding individual snips that are associated because they are recurrent in the mental state of India’s cancer population. But if it’s not recurrent, you won’t see it. So this is an idea that really kind of wanted me for quite a while since this paper came out from the 1000 Genome Project, which showed that all of us here have different faces. And the reason we have different faces is this amazing set of variation in Snips and Jermaine Snips and other genomic variations that we are born with. So an average person carries about
20 and 50 to 350 genes that have a loss of function. That’s probably the reason why I have this poor voice and small stature. But anyway, so the point is that this low frequency events that occur in unique combination individuals might set the stage that what additional events matter or cause the transformation. So it’s a combinatorial effect, right? We put these hypothesis forward that really that functional germline variants as potential Co oncogenes.
00:37:22.340 --> 00:37:24.632 And this actually I think there's
NOTE Confidence: 0.663768066666667
00:37:24.632 --> 00:37:26.960 something that covers on the screen.
NOTE Confidence: 0.663768066666667
00:37:26.960 --> 00:37:28.675 Yeah, so you can’t see this well,
NOTE Confidence: 0.663768066666667
00:37:28.680 --> 00:37:29.505 but this model,
NOTE Confidence: 0.663768066666667
00:37:29.505 --> 00:37:31.430 the the nice thing about models is
NOTE Confidence: 0.663768066666667
00:37:31.485 --> 00:37:33.649 they predict testable hypothesis, right.
NOTE Confidence: 0.663768066666667
00:37:33.649 --> 00:37:35.743 So this particular idea that the
NOTE Confidence: 0.663768066666667
00:37:35.743 --> 00:37:37.432 Germans polymorphisms all of them
NOTE Confidence: 0.663768066666667
00:37:37.432 --> 00:37:39.172 together said this theme stage for
NOTE Confidence: 0.663768066666667
00:37:39.172 --> 00:37:41.342 what counts as an oncogenic event and
NOTE Confidence: 0.663768066666667
00:37:41.342 --> 00:37:43.296 eventually this is the totality of
NOTE Confidence: 0.663768066666667
00:37:43.296 --> 00:37:45.376 abnormalities that lead to cancer.
NOTE Confidence: 0.663768066666667
00:37:45.380 --> 00:37:48.173 So it’s this sort of testable leads
NOTE Confidence: 0.663768066666667
00:37:48.173 --> 00:37:50.300 to this testable hypothesis,
NOTE Confidence: 0.663768066666667
00:37:50.300 --> 00:37:52.448 right that cancers in younger patients.
NOTE Confidence: 0.663768066666667
00:37:52.450 --> 00:37:53.440 This is correct.
They should have more germline variants because they need fewer somatic events to reach a threshold, right? The sexual disturbance that pushed them over to become malignant. And theoretically you could also use this idea to develop a cancer gene systems integrity score that captures how far a cell or tissue is from this malignant transformation. So we started to study that. And this is a paper that touching postdoc in my lab did. So we asked this really fundamental
simple thing that amazingly not a lot of people actually studied before that what’s the relationship between the person’s age of each of your diagnosis of cancer and the germline variant load in cancer relevant genes. So what are cancer relevant genes? So we just put from the literature and from review articles about 1500 genes which are experimentally validated that they alter. They’ve played an important biological role in cancer. And when you see here, it’s actually pretty obvious and it’s really beautiful, right.
So people who develop cancer at an older age have fewer germline alterations in these cancer relevant genes. People who develop cancer at younger age have a much higher, these are age bins by years of 10 and the opposite is seen in the somatic space. So people will develop cancer at their ages. Prostate cancer folks have a lot of mutations, whereas people who develop cancer at an early age have fewer somatic. and we knew this from the pediatric literature actually.
Pediatric cancers don’t have a heck of a lot of mutations. So that’s actually a really nice story that supports this idea that somehow that’s the combined effect. If you have a lot of germline hits, you need a fewer random somatic hits to push you over. In this paper view, it kind of did you think a little bit deeper and you know, so cancers which actually are highly linked to environmental factors for lung cancer for example that they actually tend to have a lot more somatic events and some somatic events and some somatic
mutations from somatic origin,

from germline in other cancers

testicular germs,
atoms are dominated by germline

So in between and some of them are

actually like testicular germs,

atoms are dominated by germline

rather than somatic hits.

So in between and some of them are

So in between and some of them are

So we asked this question whether

what’s the what’s the totality

of cancer relevant human genes

and the name we came up with the

really simple concept that if.
Core cancer genes are important and we define core cancer genes actually from a clinical panel, the MSKCC impact panel that’s clinically used to define actual permutations. So these hypothesized the genes that interact in a. Putting interaction network or the string network that there’s a lot of different ways to measure interactions. So genes that interact with the core genes will be somewhat important and genes that interact with this one step remove genes will also be important to some extent but probably less. And then those which are three four
steps removed are even less important.

So we wanted to test this hypothesis, but as you get closer to the close genes then you would have increasing connectivity.

That’s one mathematical way to measure the importance of gene as you get closer.

So one step. Both from from core cancer genes then it’s going to be more important than survivability.

We can check this in genome wide CRISPR and ASARONE screens.

Also predicted genes which are one step removed, 2 steps removed are more important than
those which are three steps removed

in terms of having large number of

somatic mutations in in Kansas and

that they will be under a stronger

negative selection in the germline,

right,

because they are important.

And in many of these genes that

are important,

cancer are important in many other things

and that’s exactly defined in this paper.

And this just shows you the numbers though.

So one or two step remove genes in

our genome is about 10,000 genes.

So actually probably the cancer 11

genes space is much much bigger,
just don’t know about a lot of these and of course they’re importance is not as important as a P53 mutation but nevertheless they contributes very likely contribute to the biological disease. So where are you going with this? So what you actually want to do really is so address cancer as a cellular transformation as a a defect in a in a complex system. So complex systems fail through unique combinations of individual non lethal events. I mean just think about this if you would run the statistics on what’s causing plane crashes,
00:42:22.210 --> 00:42:23.254 even find anything.
NOTE Confidence: 0.7001029925
00:42:23.254 --> 00:42:24.994 Because even though flying through
NOTE Confidence: 0.7001029925
00:42:24.994 --> 00:42:26.309 a storm is a risk,
NOTE Confidence: 0.7001029925
00:42:26.310 --> 00:42:27.984 but many many planes fly through
NOTE Confidence: 0.7001029925
00:42:27.984 --> 00:42:29.782 storms have any problem, you know,
NOTE Confidence: 0.7001029925
00:42:29.782 --> 00:42:31.146 pilot sleeping or not.
NOTE Confidence: 0.7001029925
00:42:31.800 --> 00:42:34.075 it’s a lot of happens that that
NOTE Confidence: 0.7001029925
00:42:34.075 --> 00:42:36.238 despite of this sort of human errors,
NOTE Confidence: 0.7001029925
00:42:36.240 --> 00:42:37.071 the plane survives,
NOTE Confidence: 0.7001029925
00:42:37.071 --> 00:42:38.733 you don’t even know about it.
NOTE Confidence: 0.7001029925
00:42:38.740 --> 00:42:40.516 So it’s really a unique combination
NOTE Confidence: 0.7001029925
00:42:40.516 --> 00:42:41.700 that brings down points.
NOTE Confidence: 0.7001029925
00:42:41.700 --> 00:42:43.359 And so that’s the thing that we
NOTE Confidence: 0.7001029925
00:42:43.359 --> 00:42:45.177 actually try to see whether we could.
NOTE Confidence: 0.7001029925
00:42:45.180 --> 00:42:46.836 So some of these unique combination
of Germany and some of the events into a score and they ultimately visualize it. They did a little bit of a sort of preliminary kind of effort in this few years ago with wavey she trying to kind of map all the molecular abnormalities that particular cancer. As and visualize it in a standardized way in these papers we try to resurrect this really delighted that Susan Coleman actually accepted this challenge for their hecaton in March next year. So we’re going to lead A-Team to to try to develop this Kansas score. Umm.
So the new classes of drugs, right.

So that’s the last piece that I’m actually going to talk to you a little bit because I’m so excited about it.

So metabolically, right, rewiring is a major hallmark of cancers, yes. Yeah, we don’t have any drugs that exploit it.

So we started off with the computational biology project to look for.

So remember, a lot of chemotherapy drugs interfere with DNA synthesis because you need to double your DNA, but you need to also double your lipids. You also need to double your proteins.

So why don’t we have drugs in that space?

So we started off with the computational biology project to look for.
Most of isoenzyme diversity in cancer compared to corresponding normal tissue. So isoenzymes kind of more or less sort of could catalyze the same chemical reaction. But they are different genes and sometimes they are located in different compartments. So what you want to look at is is a particular isoenzyme becomes cancer dominant. So this isoenzyme diversity gets lost because out of the three or four isoforms that produce the same sort of chemical reaction, one becomes dominant. That may be actually important.

Analogy.
change that the normal cell has kind of fun,
NOTE Confidence: 0.903624126666667

actually both sides of enzyme one
NOTE Confidence: 0.903624126666667

and two and the cancer actually
NOTE Confidence: 0.903624126666667

one of these becomes dominant.
NOTE Confidence: 0.903624126666667

So we asked how many are these
NOTE Confidence: 0.903624126666667

in the human genome?
NOTE Confidence: 0.903624126666667

So we again went to the TTC share
NOTE Confidence: 0.903624126666667

data and called all the human enzymes
NOTE Confidence: 0.903624126666667

which have less than 5 isoforms
NOTE Confidence: 0.903624126666667

to find to look for a pattern that
NOTE Confidence: 0.903624126666667

showed this cancer dominance.
NOTE Confidence: 0.903624126666667

Once we find this,
NOTE Confidence: 0.903624126666667

then we looked whether we can see the same
NOTE Confidence: 0.903624126666667

in the CLA the cancer cell line encyclopedia.
NOTE Confidence: 0.903624126666667

Just to make sure that this is really
NOTE Confidence: 0.903624126666667

happening at a cellular level,
00:44:54.930 --> 00:44:57.030 not at the tissue level because the TCG’s tissue level and it also then once we confirm those that they are also dominant in a cancer cell line that enabled us to really check whether this particular isoform is, is survival critical in the depth map data which is CRISPR. You have no card database. And then the final hit you wanted to confirm, so this is what we found. So there are about 136 cancer breast cancer dominant isoenzymes that we find in the CG. About 81 of these are also cancer dominant in breast cancer cell lines,
but 53 are important for survival. When you knock it out, you can sell lines, survival improves. And about 44 of these, the locking out the particular isoform is more important than knocking out the other one and then you actually meet all these three criteria then you end up with about 17 potential targetable isoenzymes in breast cancer. But we did this for a whole bunch of cancer types and the the most shared sort of cancel them in a nicer form turned out to be a C1 or acetyl coenzyme carboxylase. And this little uncertainty,
00:46:05.446 --> 00:46:08.795 the things the right side for

00:46:08.795 --> 00:46:10.370 you shows the

00:46:10.370 --> 00:46:12.274 the actual pattern expression pattern, right.

00:46:12.274 --> 00:46:14.859 So the red one is a potential target and the

00:46:14.859 --> 00:46:17.001 first column or the first sort of set by

00:46:17.060 --> 00:46:19.499 the line start is the normal tissue and the

00:46:19.499 --> 00:46:21.560 second column is the corresponding cancer.

00:46:21.560 --> 00:46:22.995 So you see that the blue goes

00:46:22.995 --> 00:46:24.309 down because it’s lost in cancer,

00:46:24.310 --> 00:46:25.630 but then the red stays up.

00:46:25.630 --> 00:46:27.390 So we actually looked at why this is

00:46:27.390 --> 00:46:29.908 happening. It’s maturation driven.

00:46:29.910 --> 00:46:31.248 And but what is a C?

00:46:31.250 --> 00:46:34.229 So C1 and C2 are actually the first literally

00:46:34.229 --> 00:46:36.788 the enzymes in fatty acid synthesis.
They pre they are immediately before fast or fatty acid synthase. They convert acetyl coenzyme to Malaya coenzyme and this C1 is actually in the cytoplasm. C2 is the mitochondrial membrane also regulates fatty acid breakdown. So if you block ACC, you block fatty acid synthesis and accelerate fatty acid burning. So it turns out that actually this wasn’t real skin of pharmaceutical companies for a long time because as a target for Nash, which is non Alcohols started because a target for Nash, hepatitis or fatty liver and it’s also
00:47:11.804 --> 00:47:13.979 actually one of the major targets for herbicides that we use in agriculture.

00:47:13.979 --> 00:47:16.160 Turns out that Pfizer actually had a drug that worked amazingly well in people.

00:47:16.160 --> 00:47:19.968 They put it through several clinical trials and they established that it actually works,

00:47:19.970 --> 00:47:22.322 it blocks the novel fatty acid synthesis as you see on that curve that ports.

00:47:22.322 --> 00:47:24.598 The percent of the noble lipogenesis was also safe,

00:47:24.600 --> 00:47:26.511 and it caused a little bit of hypertriglyceridemia and made a drop in platelet counts.

00:47:26.511 --> 00:47:28.729 You know, we play the games on 400,000, except for one thing.

00:47:28.730 --> 00:47:31.172 The percent of the noble lipogenesis was also safe,

00:47:31.172 --> 00:47:32.998 in people, it was also safe,

00:47:32.998 --> 00:47:34.006 except for one thing.

00:47:34.010 --> 00:47:36.020 It caused a little bit of hypertriglyceridemia and made a drop in platelet counts.
So the politicians, not the 200,200 thousand is actually, it’s a 50% drop. But we don’t even count this as a toxicity in chemotherapy because it’s a very safe level. Nevertheless, Pfizer felt that this warrants discontinuing the drug. So we reached out to them and we actually got the right to test this drug in preclinical models and hope to bring it back to the clinic if these little promising?
So I don’t really invitro data because the invitro, you know metabolism is highly sort of. Dependent on how much fatty acid and one that you have in the media. So this is the in vivo data in mice. So this is PBX to macros that we contracted out for Jackson lab and you see that this ACC inhibitor actually inhibits the growth although doesn’t strike completely. The MDA MB 468 Genographic did here at Yale shows the same thing but the most striking thing was synergy, the doxorubicin and Vina Robin and
also with the collaborator is interested endocrine sensitive CVD and resistance to develop the food.

Strand resistant MCF 7 cell line, she also showing you know xenograft model that there are actually inhibited the growth. So this looks pretty promising to us and we do some additional studies to really figure out more about the synergy between chemotherapy agents and we hope to get this back from Pfizer. But how does this work? So the most interesting thing was that when we looked at what transcriptional changes occur after exposure to this drug,
what really was. Striking is the that there was a dramatic increase in genes that are.

Mediating and involved in unfolded protein response and upregulate endoplasmic reticulum stress. So our working hypothesis thereby inhibiting the Novo fattiest synthesis, you actually alter the membrane composition of the endoplasmic reticulum. You know proteins have to find a threat through the membrane to get into the endoplasmic reticulum for secondary modifications and we think that by changing the endoplasmic reticulum lipid
composition we change this process.

Of of protein synthesis and in user

unfolded protein response which eventually overwhelms the cell.

So that’s the project that we do in the lab.

Look at the lipid membrane composition

of of the endoplasmic reticulum as as far as we can and the lipid alterations

in the cells exposed to this and also

some some reporter systems to nail

this as the mechanism of action.

So I’m going to summarize this really.

So for those of you who are clinical fellows,

you know every clinical dilemma

that we discussed in a tumor boards,

it’s a research question asking for a study,
some movies disheartened then

people come about saying that OK,

what should I research?

I mean what you should

research is all around us.

You just need to open your eye.

And so recognizing the prognostic

importance of Pathologic CR residual

disease has left new treatment

strategies and improved survival in

triple negative disease and her two

positive disease and I showed you how so.

Molecular offices of these issues

also gives some idea that how

we could make it even better by

research is all around us.
studying the difference between nonresponders and responders. So immunotherapy established its value in breast cancer and Robinson is now approved as as neoadjuvant therapy together with chemotherapy for all three primary disease. It’s also approved as first line therapy for PD like 1 positive metastatic breast cancer. And I think we have a reasonably decent explanation why you need the PD ligand one in the metastatic disease. So we are about to launch studies to demonstrate that similar benefit could be seen in a subset of
molecular defined subset, small subset of ER positive breast cancers. And we also have some promising markers that could actually make this whole strategy safer and more cost effective by tailoring the treatment to those who really needed it. But these you need validations and I think the most exciting sort of things on the horizon clinically is CDN surveillance and interventional homophone macular relapse that might ultimately reduce further metastatic recurrences and this understanding the molecular phylogeny of metastatic
Disease really prompted this idea because the synchronous mats are very similar to the primary tumors. They might be responding in the same way and the micro mats that remain after eradication are similar to them. So that the microbes that remain after the primary tumor is being resected may be approaching the same disease with the same strategy that we very successfully used in stage three disease. It might actually cure a small subset, maybe 10% or maybe 30%, of of the Novo metastatic stage four disease. And.
There's a really deep portfolio of new classes of drugs.

And that's my last slide.

I apologize ahead of time for people who actually didn't make it to the slide, but I ran out of space.

But these are the various people who worked in my lab and contributed the work that I showed you and students and other collaborators and collaborators within Yale.

So. If you have any questions then feel free to.
Saying that, we were going to.

And you mentioned, right and when you talked about the model especially.

Negative. I want to know if you will consider rate in that model and it’s so.

So actually Kim and and some other previous lab members did they really nice analysis trying to see whether there is a immune difference between triple negative breast cancer by race.

The hypothesis was that that. Stress and this sort of this weathering that that unfortunately many people have to suffer would have an impact on your immune immune system, right.
So the truth is that if there is such a thing, it’s really subtle. We find some really intriguing things around macrophages, but whether this really holds up, I’m not quite sure yet. So I can send you the slides and we have some things, some references there and we see some things but I’m not sure that it’s really detectable. It’s really detectable. There are other things that we haven’t looked at but we plan to do which is like inflammatory markers in the blood. But that’s also kind of
biased by comorbidities.

So if you have a lot of other diseases, then it’s just going to be high anyway.

And in terms of the models, so Pathologic CI is equally good regardless of race.

In fact, I personally have a really serious doubt that there is any major genetic sort of explanation behind disparities and outcome.

So models that include in survival rates are problematic, right, because it perpetuated a risk
factor that that maybe not true.
So if your social, social circumstances change.
Is there a question from online?
I should call you back.
So there’s this question online that.
Umm. Somebody’s relevant regretting their choice that they’re not breast oncologist and they agree with that.
That’s the do patients with inflammatory breast cancer have higher response rates to checkpoint inhibition and the agent setting regardless to applying results.
Yeah, that’s a good one.
So you know inflammatory
breast cancer is a misnomer. It's really, it's a clinical description that people came up and whatever maybe the 19th century and because the breast looks like inflamed, it looks like a skin infection and very often primary care physicians. Give it antibiotics and it just gets worse. So inflammatory breast cancer actually is not particularly rich. In fact it's pretty poor in immune cells. But we did. Actually the first whole genome sequencing of inflammatory breast cancer, hoping to find something and
disappointed we didn’t find anything that actually defined this autonomically at the DNA sequence space, but we find some interesting things. Again, TGF beta macrophage related markers show up there. As potentially contributing to the poor outcome. But yeah, so inflammatory breast cancer is all the four subtypes and as far as we can tell today, there is really no nominal genomic alteration. So what type of preventive
interventions do you foresee for patients with high cancer score.
So if you already have validated and really effective prevention drugs, right, the moxon aromatase inhibitors and food and other drugs, the I type drugs, but they have side effects and I think one way to use these cancer score would be to if you’re high risk that you are close to this tipping point, I should say you that we don’t have that score. It’s working on it. But it’s the idea that you can tell that these biopsy, tissue biopsy shows that you are
close to this tipping point and maybe you are willing to put up with some additional. 

Discomfort from a prevention drug.

A lot of times with the people who have even PCR, they can relapse in the brain. And people sort of say that’s due the blood brain barrier.

but are there molecular alterations that predict frame labs or can you?

No, I can’t. But you know, I mean, that’s the reason why I
don’t go to many of the meetings, because there are so many interesting things to study. I just enjoy them more but yeah so, so people tried that but they didn’t find it. But what you bring up is illegal one right. So the pathologic CR is really good but it’s not a perfect predictor and for there are many reasons why there should be a disconnect with Pathologic CR improvement in survival. So you can’t cure people twice. So if you enroll a lot of people that are on stage one breast cancer and the surgeon cure them, it doesn’t really matter whether
they are chemosensitive or not.

But in terms of recurrences look to Silver Point out something that many oncologists. Even breast oncologists may not be totally familiar with. So there are a number of studies that show now that the first sight of recurrence of the PCR, half of the time it’s the brain. When you have no PCR residual disease, then the brain is the first site in about 10% and it goes along with this idea that the brain is somehow a protected site. And the question is then how they
00:58:38.407 --> 00:58:40.654 actually can break this protection and
NOTE Confidence: 0.764090394
00:58:40.654 --> 00:58:42.744 really help avoid brain recurrences.
NOTE Confidence: 0.764090394
00:58:42.750 --> 00:58:44.580 There are some really good
NOTE Confidence: 0.764090394
00:58:44.580 --> 00:58:46.656 initiatives in the in her two
NOTE Confidence: 0.764090394
00:58:46.656 --> 00:58:48.511 positive space and some of the ADC
NOTE Confidence: 0.764090394
00:58:48.568 --> 00:58:50.810 may get in there triple 90 disease,
NOTE Confidence: 0.764090394
00:58:50.810 --> 00:58:53.010 but what actually would define
NOTE Confidence: 0.764090394
00:58:53.010 --> 00:58:55.391 high risk for brain recurrence
NOTE Confidence: 0.764090394
00:58:55.391 --> 00:58:57.766 in terms of molecular markers?
NOTE Confidence: 0.764090394
00:58:57.770 --> 00:59:00.426 But they could find that in a reproducible
NOTE Confidence: 0.764090394
00:59:00.426 --> 00:59:02.847 and accepted sort of widely accepted way.
NOTE Confidence: 0.9430172
00:59:06.360 --> 00:59:09.036 Thank you. Thank you for all
NOTE Confidence: 0.9430172
00:59:09.036 --> 00:59:11.618 of you who have joined both
NOTE Confidence: 0.9430172
00:59:11.620 --> 00:59:12.956 in person and virtually.
NOTE Confidence: 0.9430172
00:59:12.956 --> 00:59:15.402 This concludes our breast cancer
NOTE Confidence: 0.9430172
00:59:15.402 --> 00:59:16.906 awareness month grand rounds.
Thank you so much.

Yeah.