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 Pushki 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. He’s published over 250 scientific manuscripts in high impact medical journals.
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.

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.

I hope it’s OK with you.

It’s delighted to see that some people are in the auditorium because
I actually forgot how to get here. So I really sympathize with those of you who are actually online with this. So I think I need to start with my disclosure slides. And then before I start my slides, I would actually like to make a confession to you and admit a weakness. It’s not chocolate, but I do feel like a child in a candy store surrounded by a lot of really delicious and very interesting scientific questions.
And don’t be scared,

I'm not going to talk about all

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 are 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
NOTE Confidence: 0.88288054
00:04:31.968 --> 00:04:35.308 dig out from high dimensional genomic data.
NOTE Confidence: 0.88288054
00:04:35.310 --> 00:04:37.920 So what is the molecular phylogenetic
NOTE Confidence: 0.88288054
00:04:37.920 --> 00:04:39.225 relationship between different
NOTE Confidence: 0.88288054
00:04:39.225 --> 00:04:41.367 metastatic lesions and the primary tumor?
NOTE Confidence: 0.88288054
00:04:41.370 --> 00:04:43.205 Is these different for synchronous
NOTE Confidence: 0.88288054
00:04:43.205 --> 00:04:44.306 mats against asynchronous?
NOTE Confidence: 0.88288054
00:04:44.310 --> 00:04:46.515 That’s you know why some Kansas are
NOTE Confidence: 0.88288054
00:04:46.515 --> 00:04:48.478 immune reaction immune poor was the
NOTE Confidence: 0.88288054
00:04:48.478 --> 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
classes of drugs that we developed.

And I think the journey is just about to begin.

So how new treatment strategies could influence outcome?

So in the early 2000s, we were interested to explore period preoperative chemotherapy for women who actually had operable disease and we assumed that they would end up with a better cosmetic outcome as smaller disease.

And at that time, 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.
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% response 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.
rates by tumor infiltrating into side.

So they grouped the cases into

no lymphocytes, some lymphocytes, lymphocyte predominant and you

see that the pathologic CR rates

these numbers in the little

blood red circles increase as you

have more and more lymphocytes.

So for example in the blue, the square or highlighted

area and ER positive disease,

we know lymphocytes,
it’s a very small 6% PCR.

If you have a lot of lymphocytes,
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 that address these these issues.
So I want to share with you some results
which I think really informed a lot of
my thinking about the the value of the
role of immune system in breast cancer.
So a few years ago Anton Sofronoff
was a medical student here at. Yeah.
At that time took on this project,
but downloaded all the CG data or an
AC DNA copy number, mutation data,
germline snips and ask 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. The results are actually quite counterintuitive. So what this shows you is a correlation.
matrix of about 12 immune gene signatures that we use to define the immune presence or absence or in your richness and about 6 genomic features. So the darker brown shows a higher correlation value and the darker blue shows a negative correlation. And you see right away that the immune gene signatures are highly correlated one another, whereas they are not correlated very closely at all. In fact, they are anti correlated with many of the Economic features. So and you see this across the 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 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.
00:12:30.406 --> 00:12:32.523 evidence that there is an active
NOTE Confidence: 0.798638677142857
00:12:32.523 --> 00:12:34.647 immune editing in early stage disease, 
NOTE Confidence: 0.798638677142857
00:12:34.650 --> 00:12:34.962 right. 
NOTE Confidence: 0.798638677142857
00:12:34.962 --> 00:12:37.458 So a lot of immune cells in actually 
NOTE Confidence: 0.798638677142857
00:12:37.458 --> 00:12:38.995 called remove chromo heterogeneity 
NOTE Confidence: 0.798638677142857
00:12:38.995 --> 00:12:41.704 and that’s why you have a chromoly 
NOTE Confidence: 0.798638677142857
00:12:41.767 --> 00:12:43.975 simple tumor and actually a lower 
NOTE Confidence: 0.798638677142857
00:12:41.767 --> 00:12:43.975 your antigen load because the cancer 
NOTE Confidence: 0.798638677142857
00:12:43.975 --> 00:12:45.982 are removed by the immune system. 
NOTE Confidence: 0.798638677142857
00:12:45.982 --> 00:12:47.578 cells with the high neoantigen load 
NOTE Confidence: 0.798638677142857
00:12:47.578 --> 00:12:49.128 are removed by the immune system. 
NOTE Confidence: 0.798638677142857
00:12:49.130 --> 00:12:51.230 So that’s really attractive. 
NOTE Confidence: 0.798638677142857
00:12:51.230 --> 00:12:54.380 Hypothesis and it makes testable predictions. 
NOTE Confidence: 0.798638677142857
00:12:54.380 --> 00:12:56.980 so one prediction is that even tumor cells 
NOTE Confidence: 0.798638677142857
00:12:56.980 --> 00:12:59.720 sort of undergo medical transformation. 
NOTE Confidence: 0.798638677142857
00:12:59.720 --> 00:13:01.340 Some of it could be eliminated 
NOTE Confidence: 0.798638677142857
00:13:01.340 --> 00:13:02.420 by the immune system. 
NOTE Confidence: 0.798638677142857
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 being 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 two 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. We could actually improve the outcome by
NOTE Confidence: 0.790063143846154
00:14:56.474 --> 00:14:58.269 giving people liberalism out and eradicate.
NOTE Confidence: 0.790063143846154
00:14:58.270 --> 00:15:00.230 Micromedex and this is what they said,
NOTE Confidence: 0.790063143846154
00:15:00.230 --> 00:15:02.218 sorry you’re unable to avoid the drug
NOTE Confidence: 0.790063143846154
00:15:02.218 --> 00:15:04.365 and the monetary support at this time
NOTE Confidence: 0.790063143846154
00:15:04.365 --> 00:15:06.225 due to unclear regularly path forward.
NOTE Confidence: 0.790063143846154
00:15:06.230 --> 00:15:08.043 But it was three years later they
NOTE Confidence: 0.790063143846154
00:15:08.043 --> 00:15:09.563 actually realized that there is a
NOTE Confidence: 0.790063143846154
00:15:09.563 --> 00:15:10.949 path forward and they actually run
NOTE Confidence: 0.790063143846154
00:15:10.949 --> 00:15:12.554 both of these studies or or agree to
NOTE Confidence: 0.790063143846154
00:15:12.554 --> 00:15:14.790 do it and they to their credit they
NOTE Confidence: 0.790063143846154
00:15:14.790 --> 00:15:16.869 actually invited me back to their
NOTE Confidence: 0.790063143846154
00:15:16.869 --> 00:15:18.975 steering committee of the new adjuvant
NOTE Confidence: 0.790063143846154
00:15:18.975 --> 00:15:21.598 trial and I lead the adjuvant trial.
NOTE Confidence: 0.790063143846154
00:15:21.600 --> 00:15:23.959 So what do these studies show it?
NOTE Confidence: 0.790063143846154
00:15:23.960 --> 00:15:26.270 This is just the selection that is
NOTE Confidence: 0.790063143846154
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 this is a work that Adriana Khan, one of our fellows showed and we presented the San Antonio Breast Cancer meeting. 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 1st initial new adjuvant trials and shovel power to show improvement in PCR.
NOTE Confidence: 0.866753938666667
00:17:49.200 --> 00:17:50.970 but was woefully underpowered and
NOTE Confidence: 0.866753938666667
00:17:50.970 --> 00:17:53.224 included all subtypes to to really
NOTE Confidence: 0.866753938666667
00:17:53.224 --> 00:17:54.896 show improvement in survival.
NOTE Confidence: 0.866753938666667
00:17:54.900 --> 00:17:56.937 So this matter analysis by the FDA
NOTE Confidence: 0.866753938666667
00:17:56.937 --> 00:17:58.939 and showed very little in fact
NOTE Confidence: 0.866753938666667
00:17:58.939 --> 00:18:00.714 no relationships at all between
NOTE Confidence: 0.866753938666667
00:18:00.714 --> 00:18:02.479 improvement in PCR and survival.
NOTE Confidence: 0.866753938666667
00:18:02.480 --> 00:18:04.118 They confused a lot of people,
NOTE Confidence: 0.866753938666667
00:18:04.120 --> 00:18:05.751 but it would have to fly against
NOTE Confidence: 0.866753938666667
00:18:05.751 --> 00:18:06.770 the totally common sense.
NOTE Confidence: 0.866753938666667
00:18:06.770 --> 00:18:09.042 Observations, Taxol improved pathologic,
NOTE Confidence: 0.866753938666667
00:18:09.042 --> 00:18:11.314 sciarid improved survival receptive
NOTE Confidence: 0.866753938666667
00:18:11.314 --> 00:18:12.690 improved Pathologic CR,
NOTE Confidence: 0.866753938666667
00:18:12.690 --> 00:18:13.740 it improves survival.
NOTE Confidence: 0.866753938666667
00:18:13.740 --> 00:18:15.140 Platinum improved Pathologic CR
NOTE Confidence: 0.866753938666667
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.
00:18:43.754 --> 00:18:46.351 concept of a continuous metric of outcome or pathological response.

00:18:46.351 --> 00:18:48.948 So again in 2007 we developed this metric called residual cancer burden to capture the pathological residual disease as a continuous variable.

00:18:51.939 --> 00:18:54.250 We did that because continuous variables are more powerful to identify genes that would be associated with outcome.

00:18:56.615 --> 00:19:01.370 So 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.

00:19:01.370 --> 00:19:03.130 Another bin.
That's the minimal residual disease or RCB 1 moderate amount or CB2 and a large amount of RCB 3. But the truth is that this is really a continuous scroll and that's why we did it so.

Be teamed up the deal I spoke to investigators because this continuous sort of score, I thought actually could reveal some really interesting things about how different drugs work. So what you see here is actually a pretty cool picture of the continuous RCB scores in seven different arms of the eye spy study. 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 that the bottom panel, which is regimen 7, you have a large improvement in PCR rates, right, because the initial zero values are much higher. That’s where the curves start. But you also see a massive shift towards the smaller values across the board. If you look at the Regiment 3 on the top instead of right hand corner, then you see that that regimen also improves PCR rates. But it does it by moving the RCB 1, the little residual disease group, 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. There is an event free survival improvement. 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,
so. He entered into this race to find predictive markers that define the patients who need pembrolizumab and this is a slide from us 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,

chemistry 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

metrics are selective to identify who actually needed the panel,

So these are these one of these

metrics are selective to identify 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 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 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 than S 1418 that I,
I mentioned to you earlier.

But again,

so this study is the fascinating thing

about science is that every advance actually throws up new questions,

even more interesting questions.

A lot of people are struggling to find answers,

how you make a cold against the heart.

A lot of people are struggling to find answers,

how you make a cold against the heart.

But we thought we ask something a little bit more original and maybe something that that could be easier to crack.

And that’s the question,
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
the PCR versus those that did not.
And we find really pretty interesting
stuff that I think could lead
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
the outcome or the efficacy. Of.
You actually went pembrolizumab.
So interestingly I just put that asterisk for you to to that.
It’s so beautiful because it congruent.
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.
The metastatic microenvironment is more immuno attenuated.
Just 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 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
associated with endocrine sensitivity, this is low. So that’s the group let’s see are positive but least likely to benefit from endocrine treatment. They have sort of a higher proliferation signature which also makes sense. So they are more sensitive to chemotherapy and we also saw this in the the, the chemotherapy arms and but we didn’t really see a major difference in the immune micro in immune signature genes. So again we hope to launch the prospective 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 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 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. So 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. 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.
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.

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.
00:31:02.850 --> 00:31:05.085 when they become clinically symptomatic.

00:31:05.090 --> 00:31:06.585 So the other potentially paradigm

00:31:06.585 --> 00:31:08.458 shifting idea is really that they

00:31:08.458 --> 00:31:10.068 could cure some metastatic disease.

00:31:10.070 --> 00:31:12.070 So you have metastatic disease kind of the

00:31:12.070 --> 00:31:13.910 current dogma is that you will die from it.

00:31:13.910 --> 00:31:15.266 It may take many, many years,

00:31:15.270 --> 00:31:16.522 but ultimately people die.

00:31:16.522 --> 00:31:18.400 I’m not sure that this actually

00:31:18.455 --> 00:31:19.750 has to happen like this.

00:31:19.750 --> 00:31:21.850 So what happened in the past five,

00:31:21.850 --> 00:31:24.022 six years is that you really

00:31:24.022 --> 00:31:25.790 understood much more clearly that

00:31:25.790 --> 00:31:27.830 only that there are multiple.

00:31:27.830 --> 00:31:28.978 Different types of meds,

NOTE Confidence: 0.803463255714286
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
from somebody relapsing and having a metastatic disease. After they went through all the chemotherapies was embolism and whatnot. So curing those folks with existing therapies is a long shot, but curing those folks who never had any therapy with the combination of drugs is probably not such a long shot. 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 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,
00:32:49.710 --> 00:32:51.545 they de Novo newly diagnosed
00:32:51.545 --> 00:32:52.646 metastatic patients particularly
00:32:52.646 --> 00:32:54.399 with oligo metastatic disease,
00:32:54.400 --> 00:32:56.659 so that we could really get rid of all
00:32:56.659 --> 00:32:58.889 the known homicides and what’s left.
00:32:58.890 --> 00:33:01.383 but we can deal with micro Mets.
00:33:01.390 --> 00:33:03.086 That’s the success story that I showed you.
00:33:03.090 --> 00:33:04.780 That’s how adjuvant therapy improves
00:33:04.780 --> 00:33:06.818 survival after removing the the primary
00:33:06.818 --> 00:33:08.564 breast cancer in the lymph nodes,
00:33:08.570 --> 00:33:09.752 the systemic therapy.
00:33:09.752 --> 00:33:12.116 Washes and and and kills them
00:33:12.116 --> 00:33:13.540 at the Micromax.
00:33:13.540 --> 00:33:15.129 So I think this better than probably

NOTE Confidence: 0.774022176190476
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will hold up in stage four disease

and the vision is very simple.

So in five or ten years you don’t call these patients the oligo metastatic stage four patients stage four, but you call them stage 3C.

Because then they will be curable.

So I’m going to move on to some other projects that I also find amazing and I just wanna share you some of the results.

So why do some women develop breast cancer 20-30 years earlier than the average or median age even in the absence of any germline mutation?

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
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
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.

Polygenic risk scores that use individual snips that are individually associated with risk to a very small extent,
sum them up and you’ve made them by the risk that they confer. That’s a polygenic risk score.

However, even the best ones today using several 100 risks polygenic risk and have a lot of missing heredity in them. So they don’t explain this complete story. So we have this other idea that could the combination of non recurrent rare germline variants and cancer relevant genes determined individual risk. So because they are not recurrent. Missed them in in indigenous studies, right,
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? So. We put these hypothesis forward that really that functional germline variants as potential Co oncogenes.
And this actually I think there’s something that covers on the screen. Yeah, so you can’t see this well, but this model, the nice thing about models is they predict testable hypothesis, right. So this particular idea that the Germans polymorphisms all of them together said this theme stage for what counts as an oncogenic event and eventually this is the totality of abnormalities that lead to cancer. So it’s this sort of testable leads to this testable hypothesis, right that cancers in younger patients. 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 that each of your
diagnosis of cancer and the germline
variant load in cancer relevant genes.
So what are cancer relevant genes?
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.

Positions, 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. And if you have a lot of germline hits, you need 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 example that they actually tend to have a lot more somatic events and some somatic
mutations from somatic origin, from germline in other cancers kind of coffee. So in between and some of them are actually like testicular germs, atoms are dominated by germline hits rather than somatic hits. But then this this location OK so 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 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 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 Kansas and that they will be under a stronger negative selection in the germline, 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. 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
00:42:31.150 --> 00:42:31.800 Been trained,
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
NOTE Confidence: 0.7001029925
00:42:46.836 --> 00:42:47.940 of Germany and some
NOTE Confidence: 0.759412185238095
00:42:47.994 --> 00:42:49.961 of the events into a score and
NOTE Confidence: 0.759412185238095
00:42:49.961 --> 00:42:51.010 they ultimately visualize it.
NOTE Confidence: 0.759412185238095
00:42:51.010 --> 00:42:53.953 They did a little bit of a sort of
NOTE Confidence: 0.759412185238095
00:42:53.960 --> 00:42:55.760 preliminary kind of effort in this
NOTE Confidence: 0.759412185238095
00:42:55.760 --> 00:42:57.851 few years ago with wavey she trying
NOTE Confidence: 0.759412185238095
00:42:57.851 --> 00:42:59.790 to kind of map all the molecular
NOTE Confidence: 0.759412185238095
00:42:59.853 --> 00:43:01.949 abnormalities that particular cancer.
NOTE Confidence: 0.759412185238095
00:43:01.950 --> 00:43:04.118 As and visualize it in a standardized way
NOTE Confidence: 0.759412185238095
00:43:04.118 --> 00:43:06.763 in these papers we try to resurrect
NOTE Confidence: 0.759412185238095
00:43:06.763 --> 00:43:08.963 this really delighted that Susan Coleman
NOTE Confidence: 0.759412185238095
00:43:08.963 --> 00:43:10.898 actually accepted this challenge for
NOTE Confidence: 0.759412185238095
00:43:10.898 --> 00:43:13.158 their hecaton in March next year.
NOTE Confidence: 0.759412185238095
00:43:13.158 --> 00:43:16.189 So we’re going to lead A-Team to to
NOTE Confidence: 0.759412185238095
00:43:16.189 --> 00:43:18.990 try to develop this Kansas score. Umm.
NOTE Confidence: 0.903624126666667
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...
Most of isoenzyme diversity in cancer compared to corresponding normal tissue. So isoenzymes kind of more or less 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.
change that the normal cell has kind of fun, actually both sides of enzyme one and two and the cancer actually one of these becomes dominant.

So we asked how many are these in the human genome? So we again went to the TTC share data and called all the human enzymes which have less than 5 isoforms to find to look for a pattern that showed this cancer dominance. Once we find this, then we looked whether we can see the same in the CLA the cancer cell line encyclopedia. Just to make sure that this is really happening at a cellular level,
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.
the things the right side for you shows the actual pattern expression pattern, right. So the red one is a potential target and the first column or the first sort of set by the line start is the normal tissue and the second column is the corresponding cancer. So you see that the blue goes down because it’s lost in cancer, but then the red stays up. So we actually looked at why this is happening. It’s maturation driven. And but what is a C? So C1 and C2 are actually the first literally 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 Alcoholics started companies for a long time because as a target for Nash, hepatitis or fatty liver and it’s also
actually one of the major targets for herbicides that we use in agriculture. Turns out that Pfizer actually had a drug that worked amazingly well in people. They put it through several clinical trials and they established that it actually works, it blocks the novel fatty acid synthesis as you see on that curve that ports. The percent of the noble lipogenesis in people, it was also safe, except for one thing. It caused a little bit of hypertriglyceridemia and made a drop in platelet counts. You know, we play the games on 400,000.
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, but did the preclinical model look promising?
So I don’t really invtro data because the invtro, 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 protein synthesis and in 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 the endoplasmic reticulum as far as we can and the lipid alterations in the cells exposed to this and also 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
studying the difference between the 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 homophone macular relapse that might ultimately reduce further metastatic recurrences and this understanding the molecular phylogeny of metastatic
disease really prompted this idea

Synchronous mats are very similar to the primary tumors might be they are responding to the same way and the micro mats that remain after eradicating those are also similar to the to them.

So that the microbes that remain after the primary tumor is being resected may be approaching the same these disease with the same strategy that we very successfully used in stage three disease might actually cure a small subset maybe 10% maybe 30% of of the Novo metastatic stage four disease.
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 the students and other collaborators and collaborators within Yale. So. Yeah, so. If you have any questions then feel free to. Ask yes, silly. I have.
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 with African American or Hispanic race 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.
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 in terms of metastatic recurrence 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.
00:54:56.700 --> 00:54:58.925 factor that that maybe not true.

00:54:58.925 --> 00:54:59.985 So if your social,

00:54:59.990 --> 00:55:03.290 social circumstances change.

00:55:03.290 --> 00:55:05.690 Is there a question from online?

00:55:05.690 --> 00:55:06.760 I should call you back.

00:55:11.020 --> 00:55:13.708 So there’s this question online that.

00:55:13.710 --> 00:55:16.924 Umm. Somebody’s relevant regretting

00:55:16.924 --> 00:55:18.472 their choice that they’re not breast

00:55:18.472 --> 00:55:19.588 oncologist and they agree with that.

00:55:19.590 --> 00:55:21.738 That’s the do patients with inflammatory

00:55:21.738 --> 00:55:24.015 breast cancer have higher response rates

00:55:24.015 --> 00:55:26.361 to checkpoint inhibition and the agent


00:55:28.290 --> 00:55:29.350 Yeah, that’s a good one.

00:55:29.350 --> 00:55:30.434 So you know inflammatory

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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’s red and hot and and and swollen,

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,
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 proton 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, the moxen 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 if 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. All right. Let’s go ahead, Andrew. 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
NOTE Confidence: 0.764090394
00:58:09.000 --> 00:58:10.530 they are chemosensitive or not.
NOTE Confidence: 0.764090394
00:58:10.530 --> 00:58:12.778 But in terms of recurrences look to Silver
NOTE Confidence: 0.764090394
00:58:12.778 --> 00:58:15.130 Point out something that many oncologists.
NOTE Confidence: 0.764090394
00:58:15.130 --> 00:58:16.258 Even breast oncologists may
NOTE Confidence: 0.764090394
00:58:16.258 --> 00:58:17.668 not be totally familiar with.
NOTE Confidence: 0.764090394
00:58:17.670 --> 00:58:19.896 So there are a number of studies
NOTE Confidence: 0.764090394
00:58:19.896 --> 00:58:21.984 that show now that the first
NOTE Confidence: 0.764090394
00:58:21.984 --> 00:58:24.102 sight of recurrence of the PCR,
NOTE Confidence: 0.764090394
00:58:24.110 --> 00:58:26.196 half of the time it’s the brain.
NOTE Confidence: 0.764090394
00:58:26.200 --> 00:58:28.916 When you have no PCR residual disease,
NOTE Confidence: 0.764090394
00:58:28.920 --> 00:58:31.013 then the brain is the first site
NOTE Confidence: 0.764090394
00:58:31.013 --> 00:58:32.978 in about 10% and it goes along
NOTE Confidence: 0.764090394
00:58:32.978 --> 00:58:34.580 with this idea that the brain
NOTE Confidence: 0.764090394
00:58:34.638 --> 00:58:36.228 is somehow a protected site.
NOTE Confidence: 0.764090394
00:58:36.230 --> 00:58:38.407 And the question is then how they
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actually can break this protection and really help avoid brain recurrences.

There are some really good initiatives in the positive space and some of the ADC may get in there triple 90 disease, but what actually would define high risk for brain recurrence in terms of molecular markers? But they could find that in a reproducible and accepted sort of widely accepted way.

Thank you. Thank you for all of you who have joined both in person and virtually. This concludes our breast cancer awareness month grand rounds.
00:59:16.910 --> 00:59:17.590 Thank you so much.

NOTE Confidence: 0.53831303

00:59:38.790 --> 00:59:41.000 Yeah.