Is a special lecture in our Yale Cancer Center Grand Rounds series and it’s the Blanche Tolman lecture series. So this lecture series was established in 2012 by Doctor Marvin Sears, who I believe will be attending today as well. Dr. Sears was a long time chair and founder of Thermology and Visual Sciences at Yale and the lecture was established in honor of his mother, Blanche Tallman, who passed away from acute myeloid leukemia.
So to our delight, this was the first lecture series at year dedicated solely to hematologic malignancies and it continues to bring to Yale pioneers that have made major contributions to our understanding of the current trends and hematologic malignancies. So it is an absolute pleasure to introduce the actor Irene Gabriel today as our special lecturer. So Doctor Gabriel is professor of medicine at Harvard Medical School. She received her MD from Cairo University School of Medicine in Egypt. And she then completed her internal
NOTE Confidence: 0.797876849285714
00:01:02.847 --> 00:01:04.832 medicine training at Wayne State
NOTE Confidence: 0.797876849285714
00:01:04.832 --> 00:01:06.420 University and her hematology
NOTE Confidence: 0.797876849285714
00:01:06.478 --> 00:01:08.118 oncology subspecialty training at
NOTE Confidence: 0.797876849285714
00:01:08.118 --> 00:01:10.168 Mayo Clinic College of Medicine.
NOTE Confidence: 0.797876849285714
00:01:10.170 --> 00:01:10.818 In 2005,
NOTE Confidence: 0.797876849285714
00:01:10.818 --> 00:01:12.762 she joined in a Farber Cancer
NOTE Confidence: 0.797876849285714
00:01:12.762 --> 00:01:14.725 Institute in the field of Waldenstrom’s
NOTE Confidence: 0.797876849285714
00:01:14.725 --> 00:01:17.150 Macroglobulinemia and a multiple myeloma.
NOTE Confidence: 0.797876849285714
00:01:17.150 --> 00:01:18.086 So doctor Gabrielle,
NOTE Confidence: 0.797876849285714
00:01:18.086 --> 00:01:19.646 as you will all see,
NOTE Confidence: 0.797876849285714
00:01:19.650 --> 00:01:22.158 has risen to become one of the world’s
NOTE Confidence: 0.797876849285714
00:01:22.158 --> 00:01:23.690 leaders in the democratic field.
NOTE Confidence: 0.797876849285714
00:01:23.690 --> 00:01:25.466 Not only has she advanced major
NOTE Confidence: 0.797876849285714
00:01:25.466 --> 00:01:27.090 novel treatments to the clinic,
NOTE Confidence: 0.797876849285714
00:01:27.090 --> 00:01:29.589 but she now also focuses on early
NOTE Confidence: 0.797876849285714
detection and interception to prevent.

Regression to full blown multiple myeloma.

Doctor Gabriel has a broad background in the biology of multiple myeloma and in the bone Marinette so important in the focus on M gas and smoldering myeloma and again preventing disease and her her research knowledge expertise allow us to define both cell autonomous and bone marrow age dependent and also genetic and epigenetic mechanisms of disease progression. And we couldn’t be more excited to hear your talk today. So welcome we wish we were in person but.
This is still wonderful. And at least we didn’t have to cancel.
Yes. Well, thank you so much, Stephanie. And as you said, it’s really a pleasure and honor to be here. And I’m sorry that it’s not in person, but it’s New England and we all know how to deal with that, I guess.
So I’ll take you through a little bit of what we do in the lab and how we translated it into the clinic on the promise of early detection and interception. These are these are my conflicts of interest. So I’ll just start with a simple question that many of us ask ourselves.
In general, in every Cancer Center when you see patients, it’s because they either had symptoms and they want to see their primary care doctor or by accident, something happened in their blood works. They had a little bit of anemia, a little bit of a higher white count and that led to further workup, which led to the diagnosis of cancer and then they get referred to you. But if you think about it, this means that we are waiting for things to happen and then. We react to cancer and by chance some of those made by good luck.
have an early cancer and we can
diagnose it early and we can cure it.
But many of them actually have stage three,
stage four cancer.
And we do sit down with them and
say we may give you some treatment,
but we may not cure the disease.
And in fact if you think about it,
pharmaceutical companies as well
cancer centers put millions and
billions of dollars into developing
therapies that can change to survival
of metastatic cancer by three or four
months and we consider that. Success.
So what can we do to change that?
How can we become less reactive to cancer and be more proactive to cancer, trying to find it early before it becomes symptomatic, trying to define it early. And then by doing that you can intervene early and make a difference in the survival of those patients? Now I would probably say that myeloma is a great example of that as a potential model system for early detection and interception. We know that myeloma has a well known clinically defined precursor condition, monoclonal gammopathy of undetermined significance and then yet another.
stage of the disease that progresses just before the active cancer, sort of a stage one, stage two breast cancer if you want to call it and that’s the asymptomatic smoldering myeloma Now I was lucky enough to be. Trained by Bob Kyle at Mayo Clinic who actually coined both of those terms, monoclonal gammopathy of undetermined significance and smoldering myeloma. And he had this amazing vision because he thought that when he described those asymptomatic patients who are just walking around with a very
small tiny monoclonal protein that they should actually be watched carefully and we they may actually progress to develop the disease. And in fact, him and Jan Waldenstrom had a big discussion where Jan Waldenstrom wanted to call it benign gammopathy because those patients. Are completely benign and why would we worry them? Yet Bob Kyle was so good in thinking ahead and thinking that there is a potential of cancer development and he coined the name of undetermined significance to give it that
sense of urgency, of understanding who would progress in their lifetime and potentially preventing it. And indeed, even the name smouldering myeloma gives you that urgency that it’s going to be on fire very soon. So let’s do something about it. So indeed he had that vision. As we should think of the mechanisms of disease progression in asymptomatic people and potentially intercepting early. Now in the older days we didn’t have good drugs, we had melphalan,
Prednisone, fat chemotherapy.

So maybe intercepting early May not make sense.

And indeed the trend or the standard of care was watch and wait until people have symptoms and end organ damage and then we treat them because we have palliative care and myeloma survival is only three to five years, but now we have 30 new drugs approved. For myeloma, we have amazing responses and the question is truly can we change that thinking of disease interception at an earlier time point?

Now the other important piece to
think about is myeloma is more common in African Americans and people of African descent 2 times or even higher, more common at an earlier younger age. In fact, we know that myeloma is more common because they haven’t earlier stage of development, not because usually of an mgus transition to myeloma, not that we know of, but we don’t think that there is a faster transition from mgus to myeloma. So really understanding what causes.
Early development of MGUS in an African American population at the younger age could help us understand why they’ve developed Milo memoir, but also intercepting it early because most of those patients, by the time they’re diagnosed, the disease assessment, anemia is very common in African Americans or because of renal failure. And again, renal failure is more common. So they are getting misdiagnosed. They don’t have the World Cup. And even when they have the World Cup and the disease assessment,
they do not get the access to clinical trials and to car T and to transplant and all of the options that we have, so the survival of myeloma in African Americans. Unfortunately, it’s still very poor. Despite all of the amazing advances we have, we still have a huge discrepancy there. So potentially closing that gap would be critical for us to understand how to change the survival of Milo. So with that in mind, our hypothesis really our model is why are we doing it any different than other cancers?
If you think of breast cancer for example, you screen early because cancer screening saves lives. And I would tell you that the blood test for a serum protein Electro. Races and monoclonal protein is much easier, more sensitive and more specific and potentially much better for us because I would rather get a blood sample done than mammography or colonoscopy. It's much easier to do. But even though we with that, we don't screen for blood cancers. They're easy to screen but we don't screen for them. And even when we find the monoclonal
gammopathy is when I find mgus, and it's very common in the general population, 3 to 5% over the age of 50 or even when I find smoldering myeloma. The standard of care to date is still telling them watch and wait until you have anemia, renal failure, fractures in your bones or lesions in your bones, and high calcium, what we call the crab criteria. That would be just like telling a woman with breast cancer, DCIS, or stage one, stage two breast cancer. You know what, you're asymptomatic. Go watch and wait until you
00:08:32.078 --> 00:08:33.062 have metastases everywhere,
NOTE Confidence: 0.859871240666667
00:08:33.070 --> 00:08:34.250 fractures in your bones,
NOTE Confidence: 0.859871240666667
00:08:34.250 --> 00:08:35.725 and then I'll treat you.
NOTE Confidence: 0.859871240666667
00:08:35.730 --> 00:08:37.786 Now you'll have a lawsuit when that case.
NOTE Confidence: 0.859871240666667
00:08:37.790 --> 00:08:39.477 So why are we not getting lawsuits?
NOTE Confidence: 0.859871240666667
00:08:39.480 --> 00:08:42.680 Myeloma, when we do that exact same idea.
NOTE Confidence: 0.859871240666667
00:08:42.680 --> 00:08:44.848 So really we need to rethink the way
NOTE Confidence: 0.859871240666667
00:08:44.848 --> 00:08:47.288 we think of treatment of myeloma and
NOTE Confidence: 0.859871240666667
00:08:47.288 --> 00:08:49.524 retrain ourselves to think that’s not
NOTE Confidence: 0.859871240666667
00:08:49.524 --> 00:08:51.534 actually the right way of thinking.
NOTE Confidence: 0.859871240666667
00:08:51.540 --> 00:08:52.214 Maybe again,
NOTE Confidence: 0.859871240666667
00:08:52.214 --> 00:08:54.236 30-40 years ago when we only
NOTE Confidence: 0.859871240666667
00:08:54.236 --> 00:08:55.840 had melphalan at Prednisone,
NOTE Confidence: 0.859871240666667
00:08:55.840 --> 00:08:57.420 it was a good idea.
NOTE Confidence: 0.859871240666667
00:08:57.420 --> 00:08:59.300 Right now it may not be a good idea to
NOTE Confidence: 0.859871240666667
00:08:59.350 --> 00:09:01.366 watch and wait for those patients or as
my patients call it, watch and worry.

So how do we change that?

We have three different areas or pillars of work that we’re doing.

Both in the lab and in the clinic we said, well, let’s detect early, let’s screen early because currently most patients with mgus and smoldering myeloma are found purely incidentally.

So let’s really understand better when you screen those patients, what is the prevalence but also who will progress and who will not in their lifetime.

The next question is let’s risk stratify those patients.

The next question is let’s risk stratify those patients.
Not every MGUS we diagnose will go on to progress to myeloma. So the question is who in their lifetime will progress to myeloma because these are the ones you want to treat. And the others, you want to tell them you're OK, you're going to live a normal life without having to develop myeloma and that differential is critical so that you can truly personalize that risk stratification for patients. And then the third one is, unless you know that you can change the survival of those patients, unless you can really intercept...
and change their survival, why are you screening for it? Because otherwise you’re causing anxiety and no change. So truly I reverse it usually and say interception is more important because without interception we should not be. Training and we should not be stratifying those patients. So let’s start with early detection and why it matters. We have seen lots of nationwide studies, the first one in Olmsted County where we indeed know the prevalence of enemas in the general population.
3 to 5% over the age of 50.

But that was found in mostly Caucasian population in the area of Olmsted County in Minnesota.

So the question was, can we really detect in a much more sensitive way than serum protein electrophoresis?

And in the high risk population not in the general population, what is the prevalence of monoclonal hemoptysis and does a treaty occur in a younger age in African Americans?

So there has been some studies indicating that people of African descent as well as people with a first degree family member
are likely two to three times higher,

have a higher chance of developing myeloma.

So we wanted to ask why in high risk screen population and this was started four years ago with the help of a stand up to cancer Dream Team. Application where we started to say let’s screen in the US for myeloma and we said we will do it nationwide. So it’s online.

As you can see here, you get a QR code and if you meet the eligibility criteria, you can sign up wherever you are and we send you a kit at home.
You go to a quest diagnostic and we send us the blood sample.

And the second thing we did is we did it by mass spectrometry, which is much more sensitive than serum protein electrophoresis.

Now to do that effort, we said that we want to screen 30,000 individuals to potentially get 10% screen positive because that’s the number that from our preliminary data indicated we will have a positive number.

And then we will follow those 3000 people to understand genomics, genetics mechanisms of disease progression, immune microenvironment or non immune...
epidemiological causes like obesity,
inflammation, autoimmune diseases and of course develop therapeutics and imaging modalities for those.
People now as we started, we really had to learn to have boots on the ground to really do the effort because if you talk to anyone about myeloma, even the African American population would tell you. I didn’t even know. There is more common in the black community than in the white population. So we have to do effort to even educate
what is myeloma to gain the trust of the African American population and then start screening them. And that was a lot of effort from a team that we hired, just going to church events, understanding how to work with our Congress people like Ayanna Presley here and of course COVID hit and all our effort got shot down because you cannot do that on zoom. So it really took us a lot of effort to try and restart all of this. And indeed we just started to go back
to health fair events and restarting it while we were in COVID we said.

well let’s look at datasets and samples that are already collected in other cohorts. And this is when we turned to the mass general, Brigham, so mass general. Brigham is a huge sample collection study that’s been going on now for the last 10 years with samples as well as of course clinical data annotation from all of the partners healthcare system or MGB as we call it now. So we collected the same criteria, African-American or people of first
degree family members from 80,000 samples that we have in MGB and total enrolled so far is 12,592. We also opened a promised South Africa one where actually they’re getting almost to 2000 samples now that they’ve recruited prospectively. And we’re also going on into opening it now in Israel because of the family histories as well as many other countries that we can do. And we were screening in my lab almost 1000 samples a week and we can do even more because mass spectrometry can get to a higher throughput level.
and you can then get detection of monoclonal proteins as well as light. Machines in a very quantitative way compared to serum protein electrophoresis. In fact, we set up the normals for binding site and now we are part of their FDA approval hopefully soon for binding site. So these are just some of the numbers showing you from MGB from promised South Africa and promised us. But this is the largest number of African Americans who have been screened to date as well as people with family history and it was interesting when we saw families with 567 members.
We have MGUS and myeloma and lymphoma.

Now you start asking questions of germline events of events that really can lead to that development in an early risk population.

So this is the paper that we published last year just for the 1st 7000 people and now we're actually going on for the larger cohort.

The people with a family history of a blood cancer were 3866 and people of African descent or blacks were 2439.

Mass spectrometry is quantifiable And this is the mass spectrometry Christmas tree.
and you can also reflect it to LCMS to give you a further detection of the monoclonal protein. All of these were truly monoclonal proteins that were quantified and verified. What we found is anything above 1 gram per liter is something that you can also detect by serum protein electrophoresis because we did spap the traditional method in the sum of the samples or in almost all of the samples. If we did anything below that at .2 grams per liter, you could potentially also detected by immunofixation.
but of course you have quantification and much more sensitivity by the mass spectrometry. So we kept those terms as they are. But interestingly and I still remember it when we got the first data because we couldn’t believe it, we found another 20% of people with very small monoclonal gammopathy that were much lower than the level that we can detect by immunofixation. we confirmed it when we got the first data because we couldn’t believe it, so we reconfirmed them. Maybe these are people who have infections, so we rescreen them.
We kept going on to try and understand what this is and we finally said, well no one has they’ve ever discovered very small monoclonal proteins. Let’s let the research tell us what it is. Now we wanted to term this something separate that mgus because we really didn’t know if this is mgus or not. So we called it mgip, monoclonal gammopathy of indeterminate potential alert ship. Don’t let him have the praises of indeterminate potential. And the story goes that David Steensma
00:16:43.977 --> 00:16:47.057 is the one who coined the name chip.
NOTE Confidence: 0.77078895047619
00:16:47.060 --> 00:16:48.356 And I saw him once and he said,
NOTE Confidence: 0.77078895047619
00:16:48.360 --> 00:16:50.800 well I called chip based on M Gus.
NOTE Confidence: 0.77078895047619
00:16:50.800 --> 00:16:52.200 I was trying to imitate
NOTE Confidence: 0.77078895047619
00:16:52.200 --> 00:16:53.600 what doctor Kyle had done.
NOTE Confidence: 0.77078895047619
00:16:53.600 --> 00:16:55.496 So now we called M give based on
NOTE Confidence: 0.77078895047619
00:16:55.496 --> 00:16:57.990 chip and it keeps going round and
NOTE Confidence: 0.77078895047619
00:16:57.990 --> 00:17:01.729 round in hematological malignancies.
NOTE Confidence: 0.77078895047619
00:17:01.729 --> 00:17:04.276 mgus prevalence in this high risk population?
NOTE Confidence: 0.77078895047619
00:17:04.280 --> 00:17:06.114 So you can see here by age
NOTE Confidence: 0.77078895047619
00:17:06.114 --> 00:17:07.780 that mgip is very common,
NOTE Confidence: 0.77078895047619
00:17:07.780 --> 00:17:09.550 almost 20% of the population.
NOTE Confidence: 0.77078895047619
00:17:09.550 --> 00:17:10.522 It increases with age,
NOTE Confidence: 0.77078895047619
00:17:10.522 --> 00:17:13.004 but as you go on with age the M
NOTE Confidence: 0.77078895047619
00:17:13.004 --> 00:17:14.609 Gus proportion of those monoclonal
00:17:14.609 --> 00:17:16.522 gammopathy is increases more and then
00:17:16.522 --> 00:17:18.726 light chain mgus was actually a very
00:17:18.726 --> 00:17:20.606 small number in that population.
00:17:20.610 --> 00:17:24.514 If I just take a standard values 3% of
00:17:24.514 --> 00:17:26.224 the population in general population
00:17:26.224 --> 00:17:28.264 is what doctor Kyle had described
00:17:28.264 --> 00:17:30.490 before and that was based on Spep.
00:17:30.490 --> 00:17:35.104 If you double it because of the
00:17:35.104 --> 00:17:37.455 higher risk population which is
00:17:37.455 --> 00:17:40.178 true 6% in our population are espec
00:17:40.180 --> 00:17:42.064 That trauma too because it’s much
00:17:42.064 --> 00:17:44.017 more sensitive and can get you
00:17:44.017 --> 00:17:46.018 immunofixation than we are 13% and
00:17:46.018 --> 00:17:48.566 that’s not even accounting for the mgip.
So a large proportion of our high risk individuals have MGUS and we need to understand better why they have it, but also who would progress in their lifetime. Now in general all monoclonal gammopathy’s were associated with worse overall survival and it was not because of myeloma, it was also because of many autoimmune diseases, cardiovascular disease, many other lymphomas. So we started seeing maybe MGUS and immune dysregulation in those patients may have other effects,
not just myeloma development.

And thus lead is leading us to understand more into correlations of mgus and chip mutations, both of them cause inflammation, potentially increased cardiovascular risk. We’re trying to understand how that regulates the immune system and immune aging, how it correlates with autoimmune diseases and so many other questions. But what we were intrigued by is those M Gibbs and why were they present in many of those people. And most of those M gifts were actually IG M Mgip, not IG or IGA.
So the first thing we said. Well, maybe it’s an isotype class switch. This is the precursor of myeloma and it’s IGM positive and then it’s class switches to IgG as it progresses and this is the first event that requires the mutations. The other possibility was maybe these are lymphomas and they secrete very low levels of IGM that’s non detectable by spep and in general we don’t even screen for lymphomas by serum protein electrophoresis. So we’re under we’re not detecting enough of the cells and low grade. Performers and now we have a
technology that can be more sensitive and indeed for us to prove that, we took samples from healthy donors from two people who have mgus, one of them had mgus and mcgiff and from 2 participants who had mgip. And indeed we did first single cell sequencing for VDJ, so now for the BCR to see if they have clonal BCR in those. Patients and then of course we did gene expression profiling afterwards.
00:19:57.000 --> 00:19:59.040 with the single cell RNA sequencing.
NOTE Confidence: 0.87823653631579
00:19:59.040 --> 00:20:00.685 And what was surprising as you can
NOTE Confidence: 0.87823653631579
00:20:00.685 --> 00:20:02.699 see here for this patient for example,
NOTE Confidence: 0.87823653631579
00:20:02.700 --> 00:20:06.060 they had one clone that was all VDJ,
NOTE Confidence: 0.87823653631579
00:20:06.060 --> 00:20:08.156 the same clone and you can see that
NOTE Confidence: 0.87823653631579
00:20:08.156 --> 00:20:10.400 in this patient all of those cells.
NOTE Confidence: 0.87823653631579
00:20:10.400 --> 00:20:12.213 So this is single cell RNA sequencing
NOTE Confidence: 0.87823653631579
00:20:12.213 --> 00:20:12.990 and the blood,
NOTE Confidence: 0.87823653631579
00:20:12.990 --> 00:20:15.139 all of the cells were for one
NOTE Confidence: 0.87823653631579
00:20:15.139 --> 00:20:17.060 clone only in that patient.
NOTE Confidence: 0.87823653631579
00:20:17.060 --> 00:20:19.223 And then this second patient had two
NOTE Confidence: 0.87823653631579
00:20:19.223 --> 00:20:21.166 different clones as you can see one
NOTE Confidence: 0.87823653631579
00:20:21.166 --> 00:20:23.050 of them was very high which is the.
NOTE Confidence: 0.87823653631579
00:20:23.050 --> 00:20:25.080 The red one here and then the
NOTE Confidence: 0.87823653631579
00:20:25.080 --> 00:20:27.218 second one here in the orange one.
NOTE Confidence: 0.87823653631579
00:20:27.220 --> 00:20:29.405 And indeed we reconfirmed that
those patients, one of them was indeed an early CLL case because we did flow cytometry and because this patient had almost 60% of the cells are all clonal, we were able to do whole genome sequencing on that sample. And indeed it was an atypical lymphoma, likely a post germinal B cell lymphoma. So either DLBCL or something like a marginal zone which was MIT 88 positive and it had. Copy number alterations as you see here, chromosome 3, chromosome 18 with a gain.
of those chromosomes.

So indeed by both DNA, by protein level in flow cytometry and by RNA sequencing we were able to indicate that two of those cases were lymphomas.

Now we’re expanding that cohort to another 4050 samples with single cell RNA sequencing and then it will be followed by DNA sequencing of course if we find this positive, but that opens the door for saying we can screen also for other lymphomas.

And not just for myeloma.

And the question is what are all of those monoclonal gammopathy is
00:21:29.600 --> 00:21:31.415 doing in our general population.

00:21:31.420 --> 00:21:33.296 So to answer some of those questions,

00:21:33.300 --> 00:21:35.778 we’re moving on to other bigger cohorts.

00:21:35.780 --> 00:21:38.380 So now we’re talking to the UK Biobank,

00:21:38.380 --> 00:21:40.124 they have a half a million samples that

00:21:40.124 --> 00:21:41.678 have been collected over 20 years.

00:21:41.680 --> 00:21:44.038 We’re talking to end Haynes and

00:21:44.038 --> 00:21:46.345 trying to get samples from NHANES

00:21:46.345 --> 00:21:49.050 as you can see here 7937 another

00:21:49.050 --> 00:21:51.381 8000 and PLO another 14,000.

00:21:51.381 --> 00:21:53.069 We are also trying to see if we

00:21:53.069 --> 00:21:54.619 can get access to the million.

00:21:54.620 --> 00:21:56.825 Veterans project to all of us and

00:21:56.825 --> 00:21:58.903 many other cohorts that have already

00:21:58.903 --> 00:22:00.688 collected large numbers of samples

43
to ask big questions of what is the prevalence in high risk population,
but also what are those early monoclonal democracies doing to the general population.
And then of course we have collaborations with all link to try and look at the protein level in those patients with proteomics.
So the next step I’ll take you through is understanding mechanisms of disease progression.
If you have mgus or smoldering myeloma, you want to know what is.
My personal risk of going on to dissolve myeloma and I don’t
have in the slides here what we just published yesterday night, it just came out in Lancet hematology, a new dynamic model to understand risk of progression because we know that the current clinical criteria, 20% plasma cells in your bone marrow, 2 grams M spike, 20 light chain ratio for a smoldering myeloma are good but not good enough because they give you a 50% chance of progression in two years and that's basically like flipping a coin, 50% chance of not progressing.
So we need something better than that or to improve on it. We developed a dynamic model and now this is a risk calculator. Any patient, any physician can use the risk calculator and have the prediction of five years, 10 years, 20 years, what is my personal risk based on clinical markers. But clinical markers are assessing the tumor burden, how many cancer cells you have. It doesn’t give you the underlying biology, how fast are they growing. So we need more.
And that the dynamic model helps you because the more data you enter in the light chain increase or the M spike increase, it gives you the dynamics of tumor progression. But we need something as the genomics and immune and other factors. So here’s one of the first papers we published a few years ago where we looked at whole exome sequencing in 250 patients with smoldering myeloma. And now we expanded it of course and we found that there were three main
mechanisms of genomic aberrations. That leads to progression or that are associated strongly with progression to myeloma and these were MAP kinase mutations like ANRAS and Karas ATM and ATR and P53 mutations DNA repair pathway and of course make alterations or translocations. In fact I think that if we have Mike, we already have myeloma and potentially some of those alterations are all secondary mutations and secondary alterations that occur when you’re already going towards myeloma, when there is no coming back and hopefully these.
Will become routine in our understanding of if someone has smoldering myeloma and has one of those likely they have very high risk of progression and we should consider therapeutic interventions in them. Now what we found lately is that one, many of our patients don’t get bone marrow biopsies or serial whole exome sequencing is OK and it’s not good enough because it doesn’t give you the primary events, the translocations that occur in those patients. So this is a paper that.
00:24:55.980 --> 00:24:57.758 Just got published a few weeks ago.

NOTE Confidence: 0.833448604347826

00:24:57.760 --> 00:24:59.998 Work from Ankit and John Batiste

NOTE Confidence: 0.833448604347826

00:25:01.490 where we took circulating tumor cells, isolated them,

NOTE Confidence: 0.753337883333333

00:25:03.014 developed a method of low input DNA and

NOTE Confidence: 0.753337883333333

00:25:05.821 --> 00:25:08.082 were able to do whole genome sequencing

NOTE Confidence: 0.753337883333333

00:25:08.082 --> 00:25:10.526 from as low as 30 to 50 cells that

NOTE Confidence: 0.753337883333333

00:25:10.526 --> 00:25:12.166 you can get in the peripheral blood.

NOTE Confidence: 0.753337883333333

00:25:12.166 --> 00:25:13.558 So you can see in mgus

NOTE Confidence: 0.753337883333333


NOTE Confidence: 0.753337883333333

00:25:14.770 --> 00:25:17.283 Many of them have small numbers of circulating tumor cells and when you are able to capture them and purify them,

NOTE Confidence: 0.753337883333333

00:25:17.283 --> 00:25:19.613 you can do whole genome sequencing

NOTE Confidence: 0.753337883333333

00:25:19.613 --> 00:25:21.770 and you don’t even have to go deep sequencing because the.
Security is so good in those samples. So indeed we had head-to-head comparison of circulating tumor cells versus bone marrow cells so that you can show indeed that all of the clonal and subclonal events can also happen in the blood. And you don’t need the bone marrow biopsy, but also head-to-head comparison to fish, which is the standard of care that we have right now in myeloma, yet another 50 year old technology. So indeed, of course, no surprise there that whole genome sequencing is better than fish,
indeed it. And get you all of the translocations,
but it can get you much more. You get mutations,
you get copy number alterations, you can even get translocations
you couldn't detect by fish. And indeed because you're purifying
small numbers of cells especially in the peripheral bloods,
you can do that multiple times during the serial development of a patients progression.
So you can ask the question when the MIC clone is growing,
what is going on and when can I treat this patient.
Now I’ll move on to single cell and I borrowed this slide from Aviva. Who basically tries to tell you why do we need to go to the single cell level, and it’s basically when you do bulk sequencing, whether it’s whole genome sequencing or bulk RNA sequencing, you’re sequencing all of the cells mashed together like a smoothie. Now it tastes good, but you can’t really tell the differences between a strawberry and a Raspberry. You can’t even tell if it’s a good Raspberry versus a mutant Raspberry.
Single cell sequencing gives you that. It gives you that ability to differentiate them from each other. And of course spatial transcriptomics or spatial sequencing. Is the ultimate goal where you get the whole fruit tart and you can understand better the localization of all of those cells in the environment. So what we did is we said, let’s look at the tumor cells in the bone marrow compartment. And this is a study where we did it in collaboration with MIT and of course with the broad.
All of our work is with the Broad Institute where we said we're lucky enough in mgus and smoldering myeloma that not all of the plasma cells are actually malignant plasma cells we have some of them are normal plasma cells. So the potential here is instead of looking at interpatient variability, healthy versus cancer patients, we can actually look at the intra patient variability, healthy cells, plasma cells within one patient versus malignant plasma. And now you can ask the
questions of here are the normal plasma cells here are the malignant plasma cells from the same patient, what are the differences in them and can I understand that mechanism of early genomic events and transcriptional changes that occur with malignant? Transformation, even within the same neoplastic cells, I can find subclusters that are very different from each other. There is a proliferating cluster. There is some that have higher expression of certain genes and that can help you understand when the patient is treated, which subcluster may respond and which
one may be resistant to therapy.

Now we moved on to do even more work on that. So this was presented in Ash this year where we showed 245 samples from 234 patients. Here we did not only do the jacks. The gene expression single cell sequencing, but we also did BCR profiling on all of those patients. So now you can get with the VGA or with the BCR sequencing the clonality of those patients. So this just shows you the potential of really understanding the tumor compartment in those patients.
We’ve done the same thing on circulating tumor cells, but I’m not showing that data here. So of course with a huge number of samples, what was very interesting is indeed all of the malignant samples cluster separately. It was not surprising. We saw that before and the normal plasma cells clustered together from all of the patients and indeed the more you look at the number of cells are increasing as you go on to myeloma, the malignant versus normal compartment. But what was interesting is we compared head-to-head cytogenetics from those patients with fish or when
we have whole genome sequencing to
the single cell RNA sequencing data.
And indeed you can see that the hyper
deployed cases were confirmed, the 414,
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to know what is happening. So we used our single cell RNA sequencing to generate what could potentially be the Cytogenetic information of those patients.

So you can see here that all of the unavailable or we didn’t know what they were, we were able to reclassify them into specific cytogenetic abnormalities. And this is the confusion matrix showing you that indeed all of the unclassified we were able to get them into a 4141114 and so on. Biggest number was the hyper deployed numbers.

So that can tell you that you can use RNA sequencing to basically
00:30:23.808 --> 00:30:25.748 predict what are the cytogenetic abnormalities at the single cell level.

00:30:25.748 --> 00:30:27.748 So now you can really say.

00:30:27.750 --> 00:30:29.280 Subclusters of those patients and subclonal abnormalities and we took it even more because we have potentially the ability to identify rare events.

00:30:31.790 --> 00:30:34.300 You can now find 814 translocation extremely rare in myeloma.

00:30:34.375 --> 00:30:37.175 it even more because we have potentially the ability to identify rare events.

00:30:37.175 --> 00:30:39.978 We miss it in many patients and now we can find it with this math A and you can even look at their expression of certain genes.

00:30:39.980 --> 00:30:42.488 You can now find 814 translocation extremely rare in myeloma.

00:30:42.488 --> 00:30:44.160 We miss it in many patients and now we can find it with this math A and you can even look at their expression of certain genes.

00:30:44.160 --> 00:30:45.910 We miss it in many patients and now we can find it with this math A and you can even look at their expression of certain genes.
they don’t express other levels of other genes for example in 14.
So now you can really go into the genetics and the transcriptional changes that are occurring in those rare events.
So when you go back to also looking at the normal versus malignant cells in those patients,
you can also ask questions that are very specific to the phenotype of those patients.
we always think that CD 56 is highly expressed on malignant plasma cells.
That’s not actually true for the small numbers of 1416 and 14.
00:31:29.944 --> 00:31:30.766 20 cells,

00:31:30.770 --> 00:31:32.486 they are negative for CD 56

00:31:32.486 --> 00:31:33.910 and you can go on.

00:31:33.910 --> 00:31:36.250 So now you can really say if I’m going

00:31:36.250 --> 00:31:38.989 to develop a therapeutic target not BCMA,

00:31:38.990 --> 00:31:39.614 but others,

00:31:39.614 --> 00:31:41.486 I want to understand whether it’s

00:31:41.486 --> 00:31:43.433 highly expressed on those cells with

00:31:43.433 --> 00:31:44.701 certain genetic abnormalities and

00:31:44.701 --> 00:31:46.777 those are the patients that I will not

00:31:46.777 --> 00:31:48.890 or I will include in my clinical trial.

00:31:48.890 --> 00:31:51.729 Now moving on to the gene expression data,

00:31:51.730 --> 00:31:54.586 you can see here these are the

00:31:54.586 --> 00:31:56.780 top highly expressed or the top.

00:31:56.780 --> 00:31:58.031 Significantly downregulated genes

NOTE Confidence: 0.843883088695652
across the spectrum from mgus to smoldering myeloma to myeloma. And because again we have huge numbers of cells, you have more, you have a better ability to detect genes that really are modulated as you go on to progress like. T3 which is a leukemia growth factor as well as transcriptional factor as well as many other genes that get down regulated as you progress but also you can identify new targets potentially for developing therapeutics or new by specifics or new cartes. And then we developed a signature.
that was developed not from the normal plasma cells but from the malignant plasma cells and it was increasing as you go on from mgus to myeloma.

And that signature by NMF by non matrix factorization was able to also detect when we applied it to compass data which is the overt myeloma data, it showed us a progression free survival and overall survival difference and it could be predictive of prognostic risk in those patients. So if you put that. In those patients as well as looking at the proliferation index,
you can actually stratify the patients as low risk, intermediate and high risk even in the compass data in those patients. We then applied it to the gene expression data to all gene expression data from mgus to myeloma and indeed show that this can be predictive. So again not only genomics like DNA data that we have. Like map kinase mutations and so on can be predictive of who will progress. Now at the RNA level, we also have a gene expression profile that can be predictive of who would progress and who will not.
So moving on to the immune system, here I'm showing you that the tumor system is an ecosystem. You cannot look only at the cancer cells, you need to look at the cancer and immune cells and of course not immune cells to understand better what causes progression. So the first thing we did a few years ago is again we did single cell sequencing. Of the immune cells in the bone marrow from MGUS smoldering to myeloma. And indeed what was surprising is we found that there were compositional changes that happened as early as MGUS.
And we were shocked because we usually think that mgus is a benign disease. You're walking around, you have a very small chance of progression. Why would your immune system be so altered that it looks like myeloma? So we found T regs are increased, 16 monocytes are increased, NK cells are altered, and then later on you have further functional changes. You have loss of the memory cytotoxic CD8 cells and then you start having less granzyme K which are the earlier stem cells and more granzyme B in those patients. And this is just showing you
some of those changes. You can see here those memory excitotoxic cells almost completely depleted in patients with smoldering myeloma, sorry, with overt myeloma. So we went on to ask a couple of other questions. One is, are those changes altered if I treat someone with smoldering myeloma and can we expand that in also the peripheral blood of those patients? So this is work by Romanos, just got published a couple of weeks ago, again also in cancer cell where we took
samples from patients on a clinical trial.

With Elotuzumab limited dexamethasone 51

patients who were treated on high risk

smoldering trial and we took samples

baseline cycle nine and end of therapy.

And what we found is we

found a couple of things.

First is of course,

the compositional changes were very similar

to what you expected in our other study,

but now it’s a much bigger #190 samples.

So indeed more T regs,

more CD4 TNS and so on.

But what we found that was

interesting is a couple of things.

One,
because we had single cell TCR sequencing on all of those patients,
we found that you actually have a significant change in the
diversity of the T cells even in early smoldering myeloma.
So this is just showing you when I resample the TCR in all of those patients,
always we had a smaller diversity in the healthy compared to smoldering myeloma.
So it shrinks significantly and you would think that it shrinks because you have one clone that expands.
So the diversity is smaller and indeed. It is clonal expansion,
but it’s not just one clone, it’s multiple clones and some of them are very small.

Now, interestingly, that expansion was merely in granzyme BC8T cells. As well as T regs, and you can see it here, uh, nicely that those clonal T cell expansions were in the CD 8 terms in those patients. So that tells you the immune system is trying to react to the cancer cells, but it’s exhaustive and it cannot do a very good job in responding to those cancer cells and that could potentially be useful for therapeutic
interventions in the future, especially with TCR therapeutics as we go on.

Now, the other question we said is can we use the immune system as a biomarker? Of disease progression, can I use an immune signature that tells me this patient will respond to therapy or not? And after therapy did they normalize their immune system. So indeed we found the signature that is predictive of response which is if you are reactive to the tumor cells then you have a better chance of responding to therapy and a
long-term progression free survival. And post therapy if you normalize your immune system indeed you have a much better progression free survival and that tells us that indeed those patients. Can have that normalization of the immune system along with MRD and we’re hoping to apply that for all of the future studies so that you don’t only look for Mart, you also look for pin in those patients. And this is just showing you some of those factors specifically for grand time, as you go on to that normalization.
in those patients, now we moved on into the blood and said, can we use the blood instead of the bone marrow again in those patients. So indeed here is just showing you the volcano plot of those patients and indeed you have the same changes in the blood as you have in the bone marrow of those patients. And it mimicked exactly what happens in the bone marrow of those patients. Not only that,
if I just do another confusion plot and say give me randomly anyone who has a peripheral blood sample and I will tell you if they have mgus or not. It was very predictive in the blood by the immune cell signature that I can tell you this one is healthy, this one is mgus. Now that opened the door for us to say can we use it also for cancer screening in general. And this is something that we’re trying to develop right now. So with that we have.
which means that we have 317 new samples

that we sequenced bone marrow and peripheral blood to really ask those bigger questions of immune regulation in mgus and smoldering myeloma.

And now you can have more expression data that really defines the progression signatures because you have more samples, you can differentiate what causes progression from mgus to smoldering to myeloma, not causes what is associated with it. Hopefully causative would be all of the functional studies that we. Can do in vivo and in vitro to say
what is really causing progression

in those patients and then of

course at the gene expression level.

So at the compositional changes,

most of the things happen at mgus and then

But at the signatures of the genes you have

a huge difference in interference signaling.

You see that sudden change of granzyme

But at the signatures of the genes you have

a huge difference in interference signaling.

You see that sudden change of granzyme

B increasing and you have more of

those granzyme BCZ its cells that

are more senescent as you can see

here with their expression of KR.

One and less cytolytic.

So they’re not capable of really

responding to the cancer cells
00:39:43.576 --> 00:39:45.956 and this is just showing you how altered immune system goes on from progression from mgus to myeloma.

00:39:50.110 --> 00:39:52.702 And then again because we have so many samples, especially low risk smoldering, which we think is likely more like an mgus and some of those mgus look more like smoldering myeloma.

00:40:04.465 --> 00:40:06.550 smoldering myeloma may actually be biologically completely different. And they are intermixed with mgus and smoldering myeloma.
We have biological relevance from each other. So you can see here huge diversity changes that occur in some of the MGA samples as well as the smoldering myeloma samples in those populations. And then finally, we're starting to look at the spatial transcriptomics. But until then we started to look at the cells that basically are adhered to each other. What is close to a myeloma cell when we pull it in a CD130 is selection, and indeed we found many of the B cells, granzyme key positive cells and. Megakaryocytes were highly...
uh, you know, attached to the tumor cells indicating that there is a lot of interaction between those cells. So in the last few minutes I'll talk about clinical interception and we have done many clinical trials throughout the years, but now we're thinking of it more precisely in our interception what we call precision interception. So in the older days we have shown there is a proof of concept.
that indeed observation versus treatment is better. In progression free survival and in one case overall survival with the Lenalidomide index studies. But these were early events or early attempts. Let’s do something better than that. So our efforts are divided into early prevention, metformin, intermittent fasting, things that really prevent progression. Then we have targeted approaches, MAP kinase mutations, with venetoclax, we’re looking at synthetically salty in one queue,
abnormalities and so on.

Then we have Immunotherapeutics, vaccines, T cell therapy with carton by specifics and so on, and then novel combinations.

And we’re doing now 4 drug regimen. There are RVD, which is basically the standard of care of myeloma.

Bringing it on into an earlier setting with the idea that can we cure the patients at the earlier precursor stages and at least can we make sure that we do never develop end organ damage in those patients.
So I'll just give you a couple of examples of those trials. This one is ongoing right now, immunol prism and this is the first time we treat patients with immunotherapy in smoldering myeloma. So we chose these inclusion criteria for high risk smoldering myeloma and we’re randomizing patients 2 to 1 to tech listenable. Bcma CD3 antibody by specific antibody or landex, our first six patients were only to Christmas because the FDA mandated that we go very slowly and we do lose reduction. And then now we’re actually...
randomizing patients and we’re up to 18 patients currently either treated or going to treat soon with the primary endpoint of response rate. And I can tell you preliminary, we are not seeing the same rate of CRS. We are not seeing the same rate of infections you see in other patients and we’re seeing impressive responses in those patients. And then of course the other option is can I use the one and done cartee therapy as early as possible when you have less tumor burden and when you have better T cell response.
and potentially will this be a curative intent in our patients.
So we’re hoping to open soon the first car T therapy in early precursor settings in high risk smoldering myeloma.
And I can tell you when I submitted it to the FDA, we were able to convince the FDA to give us the Ind. And we’re hoping soon to open that trial. So with that, I hope I convince you that early detection and early interception in one disease like myeloma matters.
And hopefully this can be applied to many other diseases and we can change the survival of our patients. And I want to thank of course amazing people, the lab, the clinical teams. And our collaborators from really all over the world, but all of course our funders stand up to cancer, MRI, FLS, NIH, our collaboration with gadgets who just basically does everything with us at the Broad Institute and above all our patients. Thank you.
I mean, absolutely spectacular, incredibly, incredibly exciting. So we have doctor nefarious here as our panelist too. And maybe I have a quick question. Do you see correlations between, you know, the mutational spectrum and then the immune environment? Yeah. How do they happen? Yeah, we haven’t even started putting it together. I mean it’s it’s an so if any bioinformaticians you have, please come because we have enough data for many, many years to analyze the data. But yes, now that we have that many samples,
NOTE Confidence: 0.9464

00:44:46.120 --> 00:44:47.884 you can start asking the question

NOTE Confidence: 0.9464

00:44:47.884 --> 00:44:50.499 in an 1114 or in a certain mutation,

NOTE Confidence: 0.9464

00:44:50.500 --> 00:44:52.156 what are the immune, that’s regulations.

NOTE Confidence: 0.9464

00:44:52.160 --> 00:44:54.029 The older samples were very small numbers

NOTE Confidence: 0.9464

00:44:54.029 --> 00:44:56.100 and of course if you start subdividing,

NOTE Confidence: 0.9464

00:44:56.100 --> 00:44:58.718 if P53 haven’t foreseen, you don’t have.

NOTE Confidence: 0.9464

00:44:58.720 --> 00:44:59.450 Of data.

NOTE Confidence: 0.9464

00:44:59.450 --> 00:45:02.005 But now as we’re enlarging the cohorts,

NOTE Confidence: 0.9464

00:45:02.010 --> 00:45:04.110 we will start to see that correlation.

NOTE Confidence: 0.1186

00:45:09.990 --> 00:45:11.240 Now you wanna ask a question,

NOTE Confidence: 0.7673

00:45:11.250 --> 00:45:12.674 I think there there is a question in

NOTE Confidence: 0.7673

00:45:12.674 --> 00:45:14.539 the chat, but Irene congratulations

NOTE Confidence: 0.7673

00:45:14.539 --> 00:45:17.054 on your really tremendous success

NOTE Confidence: 0.7673

00:45:17.054 --> 00:45:19.889 and in terms of promise study,

NOTE Confidence: 0.7673

00:45:19.890 --> 00:45:23.026 I think that’s really a successful enrollment

NOTE Confidence: 0.7673
and of extensive data generated there.

In terms of potential future clinical applications, I mean terms like number needed to screen are used for breast cancer, 80 or 100 seems acceptable. What's your sense of number needed to screen potentially for high risk patients with myeloma? Or perhaps those with family history. Yeah, great question. And this is indeed exactly the question of how can we make it standard of care, what is needed for us to switch to an early detection.
I think unlike breast cancer and other solid tumors where you know that if you cut it and the patient survived in mgus, if you find it, what is the relevance, right, because we know sensitivity and specificity is very good. So that’s not the problem that we have. So that’s not the problem that we have. So I think we have thought. 

That showed that indeed interception matters because then early detection would matter and 13% prevalence is a huge number. I mean these are not numbers you
see in any other cancer right, breast or lung and all of those. So a high risk population being African American or of African descent or black or first degree family members should be such a low hanging fruit. Like you don’t need to justify numbers needed to treat with the 13% prevalence. And that’s just mgus if you add the M *** which could be the taxing lymphomas. Now we have a huge number of people walking around with early lymphomas and myelomas. And if I may just ask one more in terms of I think you put you, you had some of this in the slides in
00:46:53.173 --> 00:46:55.452 terms of you know fasting or metformin
00:46:55.452 --> 00:46:56.788 or other metabolic interventions.
00:46:56.790 --> 00:46:58.720 What’s your potential vision on
00:47:00.710 --> 00:47:02.670 you capture as mgus or early stage?
00:47:02.670 --> 00:47:03.966 What’s your current counseling
00:47:03.966 --> 00:47:05.450 that you provide? Yeah,
00:47:05.460 --> 00:47:07.134 so you know the interceptions are
00:47:07.134 --> 00:47:08.867 easy because I can give something
00:47:08.867 --> 00:47:10.553 and I can see the response.
00:47:10.560 --> 00:47:12.877 But then so many patients have this
00:47:12.877 --> 00:47:15.043 earlier factors and there’s a lot
00:47:15.043 --> 00:47:16.888 of questions of obesity microbiome.
00:47:16.890 --> 00:47:18.820 Metabolic pathways, so we're starting
00:47:18.820 --> 00:47:20.750 to do now microbiome studies.
We're starting to do metabolic changes and immune and again they come together, the microbiome, metabolomics and the immune dysregulation to lead to progression. So a lot of that effort we're starting to work on because that can also be therapeutically intervened with whether you have microbiome therapy or of course other mechanisms. And then Catherine Mayernik and Betsy O'Donnell are amazing and trying to develop other studies like that metformin, intermittent fasting, exercise and fitness things that can really help modulate the lifestyle of
00:47:51.399 --> 00:47:52.959 patients for modifications basically

00:47:52.959 --> 00:47:55.178 that can help prevent progression.

00:47:56.630 --> 00:47:58.020 Yeah, I think your former

00:47:58.030 --> 00:47:59.428 answer may have to Natalia may

00:47:59.440 --> 00:48:02.312 have answered the question in the chat um

00:48:02.312 --> 00:48:05.510 by um Manju Prasad who’s asking is risk

00:48:05.510 --> 00:48:07.490 stratification for mgas being offered

00:48:07.490 --> 00:48:10.020 to patients in the clinical setting.

00:48:10.410 --> 00:48:12.456 Yeah. So actually our publication that

00:48:12.456 --> 00:48:14.369 just came out yesterday and Nancy

00:48:14.370 --> 00:48:17.214 mythology was specifically to ask that

00:48:17.214 --> 00:48:19.308 question because many of our patients

00:48:19.310 --> 00:48:20.521 don’t have a bone marrow biopsy.

00:48:20.521 --> 00:48:21.907 So you think they have mgus,

00:48:21.910 --> 00:48:23.703 they actually have smoldering myeloma and

95
then you don’t even know and as I said the.

Clinical annotation of what is mgus

and what smoldering myeloma is so

hard because the bone marrow is patchy.

So I can have a 10% plasma cells

Pangea model was actually

6700 participants where we annotated

all of their clinical data and we

developed the clinical model of

progression based on dynamic numbers.

If they’re M spike is increasing,

If their light chains chain is

increasing hemoglobin it would freezing,

creatinine is increasing.
Remember all of those are blood things and then we added bone marrow, uh, as well as age and we did the model with or without bone marrow biopsy to help you really say if I had a bone marrow biopsy, here’s the risk, if I don’t have the bone marrow box, here’s the risk. But it was a model for all small ring model. So I would use it. It’s available online there is calculated. So look up angia and hopefully you’ll be able to find.
fact that so many of these younger patients who are diagnosed with full blown myeloma in their 30s or 40s, you'd have to conceive that there are likely have had endust from their teenage years. So I wonder if you have any germ line genomic data within the within the promise cohort or elsewhere? Yeah. So we are trying to sequence right now all of the samples which won’t even sequencing. Uh, the MGB cohort already had their smooth arrays or now they’re actually redoing whole thing security in the same samples and then of course many of those other folks had already. So you’re right, we’re trying to
actually do that all of this data.

OK, I think they’re having some static from me or from somewhere else.

Nope, it’s. OK, it may have been your computer, but let me umm,

so there this Mendez

is asking a question in the question answer.

So how do you think of

mgip compared to lymphoid,

clonal hematopoiesis and is in GIMP

and the absence of lymphoma CL and

manifestation of lymphoid cloning,

hematopoiesis and then any information

on overlapping somatic mutations.

So great question. So we work very
closely with Ben Ebert and Lachelle

weeks and others to understand really

the interlink between Chip and.

It’s hard to know whether there is

an overlap of the mutations or not.

I think we need to 1st see how many of them

do have chip and then we try to understand.

We worked with Dan Lando where we took

some of our chip samples from myeloma and

we did the single cell sequencing data,

but most of the chip mutations were

in the myeloid lineage and not

in the lymphoid lineage.

But that brings up the
lymphoid chip question.

And again until we have more data we don’t know the answer but it’s a great question.

We have another question from American Idol and I think this highlights how important is it is that we think mechanism and disease agnostic and across specialties. So Amir is of course loving you talk.

And then right we have similar similar issues in chips because MB spectrum in terms of difficulties of response assessment. And So what do you think the primary endpoint of early phase trial for high risk
00:51:50.420 --> 00:51:52.284 smoldering myeloma should be the great?
NOTE Confidence: 0.752938765714286
00:51:52.284 --> 00:51:53.594 Question, because if we wait
NOTE Confidence: 0.752938765714286
00:51:53.594 --> 00:51:54.860 for progression to myeloma,
NOTE Confidence: 0.752938765714286
00:51:54.860 --> 00:51:56.712 especially if you treat them in the
NOTE Confidence: 0.752938765714286
00:51:56.712 --> 00:51:58.060 observation arm with Rev depth,
NOTE Confidence: 0.752938765714286
00:51:58.060 --> 00:52:00.970 you’re wait for another 1520 years.
NOTE Confidence: 0.752938765714286
00:52:00.970 --> 00:52:03.085 So we do have a meeting with the FDA,
NOTE Confidence: 0.752938765714286
00:52:03.090 --> 00:52:05.941 which actually is in Madrid to ask those
NOTE Confidence: 0.752938765714286
00:52:05.941 --> 00:52:08.980 questions. What are the endpoints?
NOTE Confidence: 0.752938765714286
00:52:08.980 --> 00:52:14.802 Can we get accelerated endpoints?
NOTE Confidence: 0.752938765714286
00:52:12.050 --> 00:52:14.802 Can we look at response, can we look at RT?
NOTE Confidence: 0.752938765714286
00:52:14.802 --> 00:52:16.970 negative disease for four to five years?
NOTE Confidence: 0.752938765714286
00:52:16.970 --> 00:52:18.728 These are all great questions that
NOTE Confidence: 0.752938765714286
00:52:18.728 --> 00:52:21.104 we need answers to be able to design
NOTE Confidence: 0.752938765714286
00:52:21.104 --> 00:52:22.167 for this property. Yes.
Let me maybe go back then to the interplay between the immune system and your clone. So do you expect that if you get rid of the malignant clone, however small, that it would have an effect on the immune system?

Oh, I don’t know. That’s a great question. Will it normalize, right?

I mean, if you look at the therapy we gave to those patients and we gave to those patients and when they were MRD negative, they normalized their immune system. But the other question is
which one started first?

Is it the chicken and the egg?

And was it already an immune dysregulation that led to those clones?

Growing.

And is that already there even when you get rid of the MRI of the clone that years and years later yet another mutation will occur because the soil is fertile, right?

So I don’t know.

And I’d love to get samples, for example, from patients before they develop mgus so that we know which one happens first.
But these are all great questions that we would love to collaborate with people and answer them together.

Awesome. We have a little more Natalia. Any questions from your team?

Yeah, I mean, I think, uh, perhaps, uh, to answer amers question and perhaps a, an immune endpoint should be a potential secondary endpoint, how to normalize that immunosuppressive environment, you know what potential interventional strategies like whether it’s nutritional or microbiome or metabolomic strategies that could be,
I don’t think we pay enough attention to weight loss interventions or exercise interventions in myeloma and there’s so much. Data you made parallels Irene with breast cancer and there’s so much commonality between the diseases, the role of inflammation, the obesity etcetera. So I don’t think we pay enough attention to those kind of interventions in myeloma prevention and even relapse prevention once you have successfully treated them. Absolutely. And I think you and Betsy.
O’Donnell would really, you know, talk for hours because we’re even thinking should we use some of those new obesity drugs, right? Like, there are so many things that we can do to prevent progression and some of them may be in our hands right now.

Yeah, excellent. So we’re getting close to to running clock and I don’t see additional questions. Um, well, I’m Erin, thank you so much for this really spectacular grand rounds and congratulations on these amazing advances that are clearly, you know,
advancing prevention which is so amazing

for many patients and then treatment.

So thank you. Thank you for sticking through you know with the zoom only option.

And we look forward to you know, getting together in person and collaborating for sure.

Absolutely. Thank you again and definitely look forward to seeing you. Not in person, but this was a good alternative. Fantastic

talk, Harry. Thank you so much.