To this week’s character center Grand rounds, we have two speakers today, both from Yale will give us some exciting discussion of some of the work we're doing here.

Our first speaker is Mario Strozza busco. He’s a professor of medicine, director of the liver center. He received his medical and PhD degrees in Italy and then had a number of leadership positions at the University of Milan before joining our faculty. He’s an expert on the care of
patients with liver cancer,
is internationally known for his work and hepatology.
Liver transplantation is a member of several scientific societies in Europe in the United States.
His current research relates to the pathophysiology of biliary tract disease is repaired.
Biology of liver repair,
liver transplantation,
liver cancer in healthcare management,
and so today we’re going to hear from Mario and tell of his talk is liver cancer, clinical care and research at Yale.
So Mario, you’re up. Thank you very much, Dan, for the introduction and thanks for the Cancer Center for the Invitation Announcement. And thanks a lot for this Milo. I’m really only as a spokesperson for a group of colleagues that are interested in India in liver cancer and treating liver cancer. So I’m just the messenger. So what do we do in the liver cancer program we take? We take care of patients with liver masses either benign or malignant are,
and the two most frequent.

Primary liver cancer are able to sell cash.

You know my also called HTC and Intraparticle Angela carcinoma and I focus my talk today mostly on ATC, which is the most important primary. Cancer of the liver.

The liver is an organ which is located in the abdomen, but really here it is. The main regulator of the whole body, metabolic coma stasis, and in fact if the liver fails we actually, the patient suffered of a syndrome which is very bad.
Absolutely Poly systemic syndrome. As you can see here. And the important thing to understand is that 85% to 90% of the patient is able to sell casino. They are also cirrhotic in the liver and not only that, but if we follow a cohort of patients with viral induced liver disease either B or C for enough time, we see that the main the. When they die, most of them died with the particular casting armor as shown here. So why what the about the circus number is actually only rise
worldwide and the estimate are there. 
There are 830,000 cases recorded every year,
with the mortality that almost approached the incidents.
And why is that? Well, this is a result of a number of worldwide the epidemics that are also risk factor for chronic liver disease and among them we can mention viral appetite is B&C. You see that they the infection from viral potato is hundreds of millions of people I call is another important work by the. What is factor as it is obesity, diabetes?
And more and more, we realize that if 50 important risk factors due to inequality’s an patient population that are underserved and they have difficulties in reaching and other risk factors, smoking alpha toxin and and other as well.

And this is important to understand that the combination of risk factor increases. And actually the risk.

So in every patient that we see, we need to look for all of them.

This risk factor are distributed unequally in the world wide.

For example, aflatoxin is more frequent
as it goes in in the African continent, but if we go to the US, All told, this publication shows Nash is a main factor. It is actually we have all the respect or combining here because we have Nash with alcohol, we have appetite is C. And so on. And in fact, if we look at the distribution of the incidents of ATC in the US. We see that is actually particularly hygge about 8. Per 100,000 in the. Massachusetts, Connecticut and New York. So if we look back more. In depth into it,
we see that in the US the liver cancer incidence has increased almost three times in the last 30 years, and the mortality is increased almost two times as shown. Also in this graph on the right, if we look at the numbers and compare the number with two big, we see that in Connecticut we have a record of 480 cases per year and this is a combination between HCC and intra Patrick. Cinema also the interparticle answer carcinoma is really minority,
00:06:09.200 --> 00:06:12.840 so we have 480 new cases and $320
00:06:12.840 --> 00:06:15.557 unfortunately and this is a figure
00:06:15.557 --> 00:06:18.125 which is similar to another big
00:06:18.223 --> 00:06:21.258 killer like the pancreatic cancer.
00:06:21.260 --> 00:06:26.630 730 and 520. So what?
00:06:26.630 --> 00:06:28.590 How does the molecular
00:06:28.590 --> 00:06:31.230 pathogenesis of apples for casino?
00:06:31.230 --> 00:06:33.258 We have said it.
00:06:35.310 --> 00:06:37.722 Most of the patients have cirrhosis
00:06:37.722 --> 00:06:40.667 and in fact the main theory is
00:06:40.667 --> 00:06:42.757 that in the cirrhotic nodule
00:06:42.757 --> 00:06:45.426 there are Even so happens that
00:06:45.426 --> 00:06:47.616 brings to Korando casino man.
00:06:47.620 --> 00:06:49.517 I’m in one of these is the.
00:06:51.700 --> 00:06:52.870 Alter the.
00:06:55.030 --> 00:06:58.398 TR T promoter that basically.
NOTE Confidence: 0.8252465
00:07:01.390 --> 00:07:04.048 Blocks the ability of the liver
NOTE Confidence: 0.8252465
00:07:04.048 --> 00:07:06.381 cell under information to undergo
NOTE Confidence: 0.8252465
00:07:06.381 --> 00:07:08.776 senescence and an among them.
NOTE Confidence: 0.8252465
00:07:08.780 --> 00:07:12.408 There are other possible.
NOTE Confidence: 0.8252465
00:07:12.410 --> 00:07:14.720 But the genetic event like P53,
NOTE Confidence: 0.8252465
00:07:14.720 --> 00:07:17.030 which is basically associated with aflatoxin,
NOTE Confidence: 0.8252465
00:07:17.030 --> 00:07:18.185 better cotton imitation,
NOTE Confidence: 0.8252465
00:07:18.185 --> 00:07:20.495 and so on and so forth.
NOTE Confidence: 0.8252465
00:07:20.500 --> 00:07:22.492 But this is a scenario that
NOTE Confidence: 0.8252465
00:07:22.492 --> 00:07:24.730 is not very well understood.
NOTE Confidence: 0.8252465
00:07:24.730 --> 00:07:27.226 All we can say for now is as
NOTE Confidence: 0.8252465
00:07:27.226 --> 00:07:29.739 there are two different classes,
NOTE Confidence: 0.8252465
00:07:29.740 --> 00:07:30.991 one name proliferation,
NOTE Confidence: 0.8252465
00:07:30.991 --> 00:07:33.493 the other non proliferation that are
NOTE Confidence: 0.8252465
00:07:33.493 --> 00:07:35.430 different in terms of their prognosis
and in terms of their ability to respond eventually to immunotherapy.

So I put the cell carcinoma is a very peculiar cancer because he has a dual personality. It's a cancer in a failing vital organ and it can be seen from a biological perspective. There are inflammation induced phenomenon, oncogenic viruses, literally natural general mutational landscape and this brings to a complex tumor phenotype with the witches aggressive. It is a terror generals with a high recurrence rate.
When is Sonic Liquor point of view?

We have any plastic disease and the liver disease, and so the street.

The treatment strategy has to be tailored according both to the tumor stage and the function liver disease, this creates some of the peculiar things in that management of this disease. So we don’t have one single way to manage it that you have resection and addition therapy.

Systemic therapy still has a.
we have the possibility to transport the patient. The only solid organ that can be transplanted and most of these patients actually die because of liver failure and in fact one professional figure that is involved in this is the hepatologist. What, because of all this, different professionals involved in this treatment, the entry points usually are multiple and this multiple entry points in the system creates different trajectory for the patient with way.
Dispassion of resource is an impact on the outcome because there is a confusion and you don’t really know what the part where the patient should follow. And this is one of the reason why it is important to have a team work. So to give an example, probably will take the whole day to this guy to figure out how to change the tires, whereas the Formula One team can do it exactly in 2.5 seconds. Which is amazing and is this love? Is this out of their coordination of care? So treatment of Apple Circus nominees, coordination of care, and this is the trajectory that the
The program has followed through the year. So we started as a conference and I remember this few people with me wrong. Salom Jeff Pollack. Jeff Wayne Rubber Dam part starting this little room and then he grew to a tumor board. Thanks to Tamar Daddy and then now it's becoming a program. And maybe it's really it's ready for the next step. So when it became a program we designed in IDL structure, which is the patient can come into the system through a single point.
Still working on that aspect, and then it’s actually discussing the tumor board where they treat him, allocation happens and is allocated to the different specialty according to the best treatment are an. After that it gets follow-up because we need to treat the risk factor. We need to mind the liver. Help us some chemo prevention protocols and mirroring this clinical operation. There is also research component which is again a team effort. So where are we? So we begin with the. This is a map of the Smiler Care center OK and this is the two main site for
liver care here at again you have in hospital and the VA off without but through the recent year there was open a site in in Bridgeville with magnetic so insight in the ambari came to stand for my shift key. James Mattis T is, you know, the westerly side and soon Alan Jaffe will go to West for now. This is in combination with with the transplant team the with the transplant team with which we have a very good long standing collaboration. Now it really takes a village to treat
00:11:58.226 --> 00:12:01.116 this cancer and here you can see.
NOTE Confidence: 0.84268975
00:12:01.120 --> 00:12:03.526 Not all of their colleagues that
NOTE Confidence: 0.84268975
00:12:03.526 --> 00:12:06.149 participates and I have to say it’s
NOTE Confidence: 0.84268975
00:12:06.149 --> 00:12:08.354 it’s a real privilege to be able
NOTE Confidence: 0.84268975
00:12:08.429 --> 00:12:10.649 to work with these individuals,
NOTE Confidence: 0.84268975
00:12:10.650 --> 00:12:12.550 and they are extremely skilled.
NOTE Confidence: 0.84268975
00:12:12.550 --> 00:12:15.147 All of them are leaders in their
NOTE Confidence: 0.84268975
00:12:15.147 --> 00:12:17.878 own right are in their own field,
NOTE Confidence: 0.84268975
00:12:17.880 --> 00:12:20.414 and so the discussion that we have
NOTE Confidence: 0.84268975
00:12:20.414 --> 00:12:22.967 are so enlightening and we follow a
NOTE Confidence: 0.84268975
00:12:22.967 --> 00:12:25.061 like a structure of discussion going
NOTE Confidence: 0.84268975
00:12:25.128 --> 00:12:27.408 through and analyze the reception,
NOTE Confidence: 0.8491186
00:12:27.410 --> 00:12:28.400 the transplant candidacy,
NOTE Confidence: 0.8491186
00:12:28.400 --> 00:12:31.244 the OR whether we need to use local
NOTE Confidence: 0.8491186
00:12:31.244 --> 00:12:33.116 regional treatment like ablation,
NOTE Confidence: 0.8491186
00:12:33.120 --> 00:12:33.968 criminalization, radiation.
It’s I don’t have the time to go into this, but it’s every single all of this possible treatment is very complex and the decision making is even more complex because it depends from systemic and local factors, and in fact we really an. We basically follow the Barcelona Liver cancer treatment, which is a. Used by master Lever Societies an but it really has a lot of troubles. OK, there are changes. This is the latest version and takes into account liver function, performance status and then
atomic location of the cancer.

But really there are lot of troubles and we cannot be so strict with the categories and for example this was written in 2019. Now the first line treatment cannot be only confined to patient at about to die, as in this staging system, so a lot of things have changed and that made difficult by the fact that we have multiple theology at the underlying liver disease. The frequent comma abilities in fact, this is a cancer.
That picture above 65 years of age.

Multiple treatment option and 70% of them have a recurrence of the cancer in the next 20 months.

We have liver transplantation and other actors, so the only way to maintain a. Structure approach this is to is that room and board with four hours is not a way where we present strange cases is really the machine. Ann and the credit for this goes to my colleague and friend to Mark Addy, who set it up and now we discussed 13 cases each week.
Last year we even with the kovit

we discuss 520 cases and one of the

busiest actually tumor Board 2 of

200 of them with new cases we have.

300 patient and follow up.

150 new cases and these actually

treated in several different ways,

but this is not the venue to to go

through the volumes or to their substantial.

The tumor board is also where we

got ideas for research and ideas

for improvement and innovation.

This is that list of items that we

discussed at the last steering committee.

For example,
not going to read all of them, but.

Generate. Recent opportunities.

Anne Anne, Anne,

Anne and also great care I I wanna
go briefly through this case.

This was a patient. Refer to doctor.

She’s key for transfer evaluation

Mike so the patient realized that

he had actually liver cancer.

And Moran had infiltrative

hepatocellular carcinoma with with

the tumour portal vein thrombosis.

So we discussed the case at the

tumor board and it was decided that

there was no other option rather than
medical treatment or offering a trial.

Stacy did try to give him softening by the beginning I, but this was denied by the insurance and so it happened at Stacy. Adjust open atrial at the initial trial with a diesel Bev, which is now you know, the first line treatment for back in that time was actually we were very lucky that we could offer him and as you see here. In the graph of plotting the alpha fetoprotein, he had a complete response. But in the next two years,
00:16:24.020 --> 00:16:26.090 this patient was completely and the quality of life of this patient, which was completely altered by recurrent severe episodes of portosystemic several opathy.

00:16:29.794 --> 00:16:31.574 As you can see here from the ammonia and actually in during one of these emission it also discussion about goals of care was initiated, so we had a patient who was treated by so we had a patient who was treated by with you from this malignant tumor. But he was dying because I believe very bright hepatologist wanagas.2 very bright hepatologist wanagas intervals with system are in, this is an act.
00:16:56.540 --> 00:16:58.121 another is stalled.
NOTE Confidence: 0.8041078

00:16:58.121 --> 00:17:00.756 Slacker, which is an interventional
NOTE Confidence: 0.8041078

00:17:00.756 --> 00:17:01.810 hepatology calling,
NOTE Confidence: 0.8041078

00:17:01.810 --> 00:17:04.966 decided to embolize his plane arena.
NOTE Confidence: 0.8041078

00:17:04.970 --> 00:17:08.132 Shanta and now the patient is
NOTE Confidence: 0.8041078

00:17:08.132 --> 00:17:10.160 functional cancer free, happy.
NOTE Confidence: 0.8041078

00:17:10.160 --> 00:17:12.800 And when he refers to what
NOTE Confidence: 0.8041078

00:17:12.800 --> 00:17:15.080 happened with the insurance,
NOTE Confidence: 0.8041078

00:17:15.080 --> 00:17:17.210 he quotes wisdom churches saying pessimist
NOTE Confidence: 0.8041078

00:17:17.210 --> 00:17:19.320 sees difficulty in every opportunity,
NOTE Confidence: 0.8041078

00:17:19.320 --> 00:17:20.856 an optimist sees opportunity
NOTE Confidence: 0.8041078

00:17:20.856 --> 00:17:22.008 in every difficulty.
NOTE Confidence: 0.8041078

00:17:22.010 --> 00:17:25.026 So this is a case which we learn
NOTE Confidence: 0.8041078

00:17:25.026 --> 00:17:28.165 a lot about it an an in fact.
NOTE Confidence: 0.8041078

00:17:28.170 --> 00:17:28.954 Now particularly,
NOTE Confidence: 0.8041078

00:17:28.954 --> 00:17:29.738 you know,
one of the things that was interesting in the Gary case was that he never had a recurrence an will. I said occurrences, something that playing sour patient 6070% of them in there. In their first two years, so that prompted the opening of a try again by Stacy and D'istria will actually try to address the role of adjuvant treatment after surgery or ablation. Another tria is being brought here by David Madore. Fu actually addresses and
other nuances of this,

so his aim is to understand whether there is a benefit in what we call combination treatment.

So the idea to combine came embolization with the.

Even on Koleji, in combination with a PKI. And another important aspect of the

program is the fact that we really tried to record and measure the outcomes.

Ariel’s affair with John awfully.

My tarantula Shapiro at there are curating a database of 1000 patients in India and the survival code divided by BCSC states that you see, here are our own.

Outcomes so we can really.
00:18:54.900 --> 00:18:57.138 Make the termination letter based on.

00:18:57.140 --> 00:18:58.985 Now our environment in expertise

00:18:58.985 --> 00:19:01.230 and is simple example that the

00:19:01.230 --> 00:19:03.252 outcome is outstanding up to more

00:19:03.252 --> 00:19:05.566 than three years for this campaign

00:19:05.566 --> 00:19:07.210 patient with initial cancer,

00:19:07.210 --> 00:19:09.891 things are changing after this an and

00:19:09.891 --> 00:19:12.886 there’s a lot to be discussed in among

00:19:12.886 --> 00:19:16.159 these patients and I I don’t have it here,

00:19:16.160 --> 00:19:18.398 but if anybody has a doubt

00:19:18.398 --> 00:19:19.144 about transplantation,

00:19:19.150 --> 00:19:22.444 I can tell you that the code was transfer

00:19:22.444 --> 00:19:25.448 stations like this so outstanding long term.

00:19:25.450 --> 00:19:28.530 Result for the few patient again get it,

00:19:28.530 --> 00:19:30.460 but this is a very,
very important aspect of what we do
an it’s going to be so complex
in fact Julius with Jim Duncan
Manderly and John actually very much
involved in trying to understand
the use that we can have artificial
intelligence in the diagonal.
This characterization treatment of this
Council and we expect that this would
be a great aid to our decision making
and also discovery of new approaches.
So what the liver cancer program
doesn’t have a formalized?
Visas program but is actually
the assembly of of several
different interested people.
What have we done to.

Put together these people so the first thing that we have been doing with Julius De Mar is these liver cancer talks their monthly in the late late afternoon on Thursday. Each of them with two or three percent Asia and this has to be ongoing. Research are now published work. It covers all the aspects, clinical, translation and healthcare and this actually this approach Spark collaboration. There were paper grant application and also a big step. Forward was at last October when again.
with the help of the Miami Justice Ann, and thanks to the help of Gary Honeycutt’s and his team in the Cancer Center, we put forward the first liver cancer Super Summit which is called pre because he was not in person. Where was Virtu are, but the mission was to address the Uncle logic challenges or liver cancer to the collaboration amount of abide. Spectrum will be a faculty. And I’m gonna really run through some of this visa suspect and what in what I call the Commonwealth to liver cancer is at yeah OK because it’s not again formalized structure,
but is the gathering of interested people coming from the medical school, the School of Public Health? the VA system involving departments like surgery, internal medicine, the Cancer Center, the year, liver cancer, the Department of Pathology and so on and so forth. But all these people actually. In a 2019-2020 publish it 72 papers, 38 of them original article position paper 14 reviews and 14 of them are actually publishing in journals with an impact factor around or above 20,
which I think is pretty remarkable.
So just a very quickly glancing through it.
The number of our faculties are actually involved.
In studying the different risk factors that I mentioned before, so we have outstanding work performing virally theology, interaction with aging, the HIV. We have food program that addresses the obesity, diabetes and affolder alcoholic liver diseases in other regions branch which is growing an Ann and also health care disparities.
An for example.

Razor, ocean and other faculties are addressing.

Some of the differences that we see even in Connecticut.

So for example, as you can see here.

The incidence of HCC is clearly higher in this panic and black population and hopefully will try to nail down what the causes are.

So outstanding results in outcome research, mostly addressing the role of surveillance and all of.

Antiviral treatment and the growing group of faculties are
also interested in concert cost,
NOTE Confidence: 0.8397243
effectiveness and care delivery.
NOTE Confidence: 0.8397243
We do a lot of things,
NOTE Confidence: 0.8397243
but we don’t really know their value
NOTE Confidence: 0.8397243
in terms of cost effectiveness,
NOTE Confidence: 0.8397243
so this is another growing area.
NOTE Confidence: 0.8397243
Translation studies that also growing and
NOTE Confidence: 0.8397243
just to mention several faculties in Basic,
NOTE Confidence: 0.8397243
more basic studies are interested
NOTE Confidence: 0.8397243
in the transition between Nashville,
NOTE Confidence: 0.8397243
roses and and cancer and in human
NOTE Confidence: 0.8397243
Hansa ran and a lot of people
NOTE Confidence: 0.8397243
is actually interesting in the.
NOTE Confidence: 0.8397243
Role of the tumor micro environment.
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Which this is, I think,
NOTE Confidence: 0.8397243
is very interesting.
This is staining for Alpha, SMA, identifying fiber, cancer, associated fibroblasts in cholangiocarcinoma and in hepatoma. You see two very different. Pathology Ann and these are correlated to two very different aggressiveness. Also the tumor let me very briefly mention some of our work in the macroenvironment or the calendar carcinoma. Showing the central role of calf or determining several of the aspects of the two Moran now our Co.
colleagues are addressing this

using single cell transcriptomics.

This is also an interest of our colleagues in radiology.

They’re trying to use.

The tools of radiology to generate reliable imaging biomarkers for immunotherapy.

This is I, I think, it’s granted or or or proposed for the NIH by David matter of MGM Duncan interest on the metabolic aspect is also.

Followed by by Michael Nathanson, lab, and here is work from Emma tells where I’m like nothing.

So I’m looking at the IP3 receptor and mitochondrial functionality in 80C and CCA,
and they're all in the chronic effect like existence of up doses generating up talking factor of this was published very well last year and and finally mentioning. Tell you who, just join and the chair of pathology is, you know, a very well renowned liver cancer researcher and is doing several things. Among this he explaining to detect circulating metallated DNA as an early diagnosis. Wait, you see, and we're really looking forward very much to this study is an an also.
He is trying to use Kartiana Glypican 3 as a target. Hopefully not that big of a TC. And I'm gonna finish now because the time is over. But you know this is just an example of the richness of the research that we have. And really this is and I have to thank all the department that are involved in this enterprise and. You know each of these department. There are some hepatologist hiding there and this is what will I call your liver, there and this is what which is a very old tradition. Here is going to celebrate
the Diamond Jubilee.

Next year and I thank you for your attention.

Thank you very much, Mario.

Very interesting talk. Are there any questions from the audience?

I can start with one.

So recently drugs have been developed that will cure hepatitis C virus.

I can start with one.

So recently drugs have been developed that will cure hepatitis C virus.

I can start with one.

So recently drugs have been developed that will cure hepatitis C virus.

People are being treated by these drugs.

And what’s the effect on liver cancer?

Tell the the strategy would be worldwide application of of HPV and therefore I would say that a growing
amount of patients she is being treated should be treated that has had like a slowing down during the COVID crisis but should resume full time. The question of the effect on liver cancer is a very good question because there has been a great controversy because a lot of patients. After eradication of the virus, have the path surprised that delivered Carson happens. Anyway, this is happening in patients that were treated already with significant fibers in their liver. And it was initially proposed that actually the allocation of
the virus would get rid of some kind of beneficial information, but further studies have shown that actually the risk is decreased, but it’s not zero. So why is not zero is something that we need to understand. My personal opinion is that we are simply eliminating one of the many risk factors. You know the regular guy is a guy that didn’t know to have actitis is a little overweight, has smoked. Is drinking, you know, not drunk but enjoying the wine.
It just doesn’t know it an an therefore yeah, you ever you have four risk factor of which you eliminate one? This is why this is a internal medicine. This is right because you really have to address all the risk factor in every single patient. Otherwise, you may fail like the eradication of appetite is C shows in certain patients and so the basic clinical recommendation is that the patient that you were ever advocated while he was erotica still needs to undergo the six months. Screening and surveillance for ACC.
Are there other other questions?
OK, with that I do see the vineyard behind your folder there in moderation.
Yeah moderation, OK thank you.
Thank you very much.
Thank you, thank you.
So our next speaker today is Jonathan Levinthal.
So Jonathan is assistant professor of Dermatology and the director of the Yale Uncle Dermatology Clinic.
He received his MD degree from New York University and is residency here at Yale.
He specializes in caring for patients with skin cancer, beginning with skin screening programs to detect cancers and sun damage and optimize prevention and therapy. The clinic serves a dermatologic needs of cancer patients dealing with a variety of skin issues, including skin changes due to chemo therapies, can infections. Cancer involvement in the scan, radiation, dermatitis, and other changes due to radiation, so we’ll hear that today. So Jonathan I’m looking forward hearing you talk. Thank you.
Thank you so much and it’s a real pleasure to be here today.

So today I’m going to talk about dermatologic conditions in cancer patients, and I’m going to provide updates from the ankle dermatology program.

So here is a list of my disclosures, mostly from serving on advisory councils with fellow Aqua dermatologist throughout the country looking at skin toxicities as well as some clinical trial research funding.

So the objectives of the talks I wanted to start by introducing you to the Aqua dermatology program.
Then I wanted to discuss the importance of cutaneous toxicities and how they can impact patients' quality of life as well as their cancer therapies. When severe, I wanted to highlight some of the most common toxicities that I see from select targeted and immune checkpoint inhibitors and also traditional chemotherapy. As well and discuss the role that aren't with their mythology. So for some background, the Uncle Dermatology program was established by my great mentor and friend, Jennifer Choi.
Shortly after she graduated residency and then I had a great opportunity when she got recruited to Northwestern as a chief resident to start seeing patients in the clinic for which I’ve led the clinic ever since. And we’ve really seen a tremendous outgrow of support from so many colleagues in Metanx terjung Radon, an anthology, and the clinic has really grown dramatically over the years. It’s a very robust, busy clinic. Some days we see up to 50 patients. And I just have a great team of
nurses residents as well as research fellows and support from the Yale Center for Clinical Investigation. So the field of supportive Oncology really blossomed in the 1990s with the advent of many different targeted kinase inhibitors, which skin toxicities were so common in almost the majority of patients and it really encompasses many different things that we service, so there's definitely all the toxicities that we see from the systemic therapies, radiation therapies, graft versus host disease as well as complications from cancer.
00:32:43.280 --> 00:32:45.260 Going to the skin with metastases,
00:32:45.260 --> 00:32:47.640 but there's really a lot of other
00:32:47.640 --> 00:32:49.356 indirect complications that we treat
00:32:49.356 --> 00:32:51.276 in clinic and that includes paranoia.
00:32:51.280 --> 00:32:54.529 Plastic disease, infectious complications,
00:32:54.529 --> 00:32:56.317 especially in patients who are
00:32:56.317 --> 00:32:57.692 part of the survivorship program.
00:32:57.700 --> 00:33:00.268 For many patients who have
00:33:00.270 --> 00:33:02.140 survived cancer now,
00:33:02.140 --> 00:33:03.636 cutaneous carcinogenesis and then
00:33:03:636 --> 00:33:05.737 also part of the umbrella is that
00:33:05.737 --> 00:33:07.329 the Melanoma program I'm part of.
00:33:07.330 --> 00:33:09.376 It falls under the umbrella of
Uncle Dermatology and so a lot of what I do is also high risk in cancer screening to diagnose and treat many different types of skin cancers and also collaborate with the cancer genetics program to obtain tissue for genetics.

So wanted to start by discussing the cutaneous toxicities are not just cosmetic. These are really important issues that impact patients quality of life and there's been many studies over the years looking at validated quality of life surveys.
toxicities to impact in both physical as well as emotional domains and so one interesting concept is that women seem to be affected greater than men in terms of their quality of life and it’s probably because of the types of regiments they did receive for breast and. Other gynecological cancers which frequently impact the here in the nails, and so this can affect women’s self image, cultural identity, sexuality as well as mental health, and a loss of control over their body.
The hallmark examples are chemotherapy induced alopecia, which we see from the cytotoxic agents, in particular an one homework study, showed that almost 60% of women with breast cancer preparing for chemo considered this to be the worst possible associated side effect and almost 10% even considered declining treatment in fear of it. So these are real, very real and important issues, and there’s been so many other studies looking at the acne reform, ranch hand, foot rashes, nail changes in mucus, itis,
all of which I’m going to discuss in which can impact quality of life.

So the study on the left kind of highlights an important concept that it’s not just those main toxicities that can impact patients quality of life. In this study of targeted agents in breast and colorectal cancers, you’ll see that things like itching, dryness of the skin, easy bruise ability, pigmentary changes, they can all be associated with poor quality of life and the study on the right looked at different types of chemotherapy and
how they impact quality of life. And not surprisingly.

A lot of the more novel, targeted therapies, especially the EGFR inhibitors, were associated with an increased number of skin toxicities, but also those which impact quality of life greater than some of the traditional chemotherapeutic agents. Unfortunately, early dermatologic intervention can really make a difference, and so Uncle dermatology programs have been showing up at most of
00:35:33.801 --> 00:35:35.631 the premier cancer centers in
NOTE Confidence: 0.82286793
00:35:35.631 --> 00:35:37.300 the States and abroad,
NOTE Confidence: 0.82286793
00:35:37.300 --> 00:35:39.860 and one study from MSK show that with
NOTE Confidence: 0.82286793
00:35:39.860 --> 00:35:42.050 outpatient Uncle dermatologic involvement,
NOTE Confidence: 0.82286793
00:35:42.050 --> 00:35:44.140 patients on immunotherapy were less
NOTE Confidence: 0.82286793
00:35:44.140 --> 00:35:46.230 likely to have interrupted treatment
NOTE Confidence: 0.82286793
00:35:46.294 --> 00:35:48.390 5% versus 30% to those managed
NOTE Confidence: 0.82286793
00:35:48.390 --> 00:35:49.578 without dermatologic intervention.
NOTE Confidence: 0.82286793
00:35:49.580 --> 00:35:51.998 In a recent study by the
NOTE Confidence: 0.82286793
00:35:51.998 --> 00:35:53.610 Harvard Group similarly showed.
NOTE Confidence: 0.82286793
00:35:53.610 --> 00:35:55.030 The inpatient konsult can also
NOTE Confidence: 0.82286793
00:35:55.030 --> 00:35:56.450 decrease the chance of patients
NOTE Confidence: 0.82286793
00:35:56.496 --> 00:35:58.168 receiving systemic immune suppression
NOTE Confidence: 0.82286793
00:35:58.168 --> 00:35:59.840 and immune therapy discontinuation.
NOTE Confidence: 0.82286793
00:35:59.840 --> 00:36:00.185 Now,
we haven't performed a comparative study.

We did perform a very large study recently that was published of over 100 immunotherapy.

Rash is 1/4 of which presented to my clinic, often with disruption of immunotherapy.

But with early dermatologic intervention, over 90% of these patients were able to remain on their treatment, so I think these numbers are compelling.

So wanted to start by focusing on some of the toxicities that I see from targeted therapy.

I mean there's so many different types of agents to discuss, I think I'm just going to
NOTE Confidence: 0.82286793
00:36:31.686 --> 00:36:33.580 review some of the main ones.
NOTE Confidence: 0.82286793
00:36:33.580 --> 00:36:35.596 In the interest of time so the EGFR inhibitors are a class that are commonly
NOTE Confidence: 0.82286793
00:36:35.596 --> 00:36:37.922 associated with cutaneous toxicities.
NOTE Confidence: 0.82286793
00:36:37.922 --> 00:36:39.334 Not surprisingly, as the epidermal growth factor receptor is expressed in the skin,
NOTE Confidence: 0.8393097
00:36:41.664 --> 00:36:45.314 hair and nails, and really important for homeostasis and some of the monoclonal antibodies likes to talk some mad panitumumab as well as the 1st and 2nd generation drugs.
NOTE Confidence: 0.8393097
00:36:49.184 --> 00:36:51.115 Fortunately, the third generation
NOTE Confidence: 0.8393097
00:36:53.930 --> 00:36:55.405 in the majority of cases.
NOTE Confidence: 0.8393097
00:36:55.410 --> 00:36:56.610 Unfortunately, the third generation
drugs like OC murdered him
NOTE Confidence: 0.8393097
for a lung cancer patients.
NOTE Confidence: 0.8393097
They don’t seem to get the rest,
NOTE Confidence: 0.8393097
the rest nearly as often,
NOTE Confidence: 0.8393097
probably less than 30%,
NOTE Confidence: 0.8393097
and so the most common toxicity
NOTE Confidence: 0.8393097
that we see is the papulopustular
NOTE Confidence: 0.8393097
for the acne or form rash,
NOTE Confidence: 0.8393097
and this usually manifests on patients face,
NOTE Confidence: 0.8393097
scalp, chest and back.
NOTE Confidence: 0.8393097
Although it could be widespread
NOTE Confidence: 0.8393097
and one common misconception is
NOTE Confidence: 0.8393097
that it’s just a sterile technique.
NOTE Confidence: 0.8393097
Reform drug eruption, which is true.
NOTE Confidence: 0.8393097
However,
NOTE Confidence: 0.8393097
I find a large percentage of these patients.
 Especially when they get to higher grades often have coinfection with staff. Both M RSA an MSA, so that’s a good therapeutic Pearl to obtain wound cultures and hear examples of the Packers and pustules. Note all this year is crusting. It was all in petition eyes with staff. Oreius is a more typical scenario in one of the more robust severe toxicities that might require more aggressive treatment, which I’ll discuss. We see lots of nail infections paronychium and because of the
piercing of the nail plate into

the hyponychium patients can get

this friable granulation tissue known as pyogenic granulomas.

These can be exquisitely tender and painful and definitely impacts patients quality of lights.

It’s not uncommon to see her growth abnormalities, including elongated eyelashes.

Some patients have a hard time trimming their eyelashes, which are curving inward and irritating their eyes, so they’ll just see me analysis

them with with cutting their
00:38:13.373 --> 00:38:15.893 eyelashes we see lots of dryness and painful cracks and fissures too.
00:38:17.750 --> 00:38:19.330 There is an example of, you know a patient who presented with a neck near former option which was in petition eyes with staff.
00:38:21.058 --> 00:38:23.288 She responded quite well to Doxie, cyclin topical steroid ointments, antibiotic ointments.
00:38:25.322 --> 00:38:27.226 And I’m a big fan of antiseptic soaks like aluminum acetate removed a serious crusting.
00:38:29.130 --> 00:38:31.069 Here’s another example of a patient.
00:38:32.725 --> 00:38:35.760 Also recently from the Lung Cancer Group who also had quite a severe a serious crusting.
00:38:35.760 --> 00:38:37.380 Also recently from the Lung Cancer Group who also had quite a severe a serious crusting.
acne deformed mesh occasionally in very severe circumstances there can actually be associated alopecia as well.
She responded very well to dermatologic intervention.
I wanted to highlight that.
While the acne reformers typically presents during the first few weeks on the head, chest and back,
we have seen uncommon presentations as well, which are described in the literature and those are prepared drug eruptions which likely fall into the category which likely fall into the category of the late acne reform toxicity.
In these cases usually present many months into treatment,
and they often present on the lower extremities in the buttocks, and as you can see with these perperek looking lesions, and they’re also frequently infected with staff on Moon culture.

Here’s an example of a patient with head and neck cancer who responded to dermatologic intervention.

And here’s an example of a patient who has pretty typical pyogenic granuloma with Paronychium, who responded to the topical beta blocker timolol gel. Many of these cases are non responsive.
to conservative approaches and sometimes procedural intervention may be required, like using silver nitrate to court arise these granulomas or even nail avulsion for the really recalcitrant cases will do. So there’s many hot topics around EGFR inhibitors one over the years has been looking at pre emptive versus reactive therapy and there’s various phase two trials which have shown that doc see cycling Minocycline with with topical steroids and moisturizers can actually reduce the severity of the rash. The overall incidence is probably not affected and I think the approach towards the rest differs depending on the program.
Here they’ve been looking at lots of new novel approaches for treating the rash, none of which are really gained widespread use. Some of the data is very mixed with these drugs and so we definitely need New approaches and then I just wanted to briefly mention that there’s a few clinical trials which we’re doing here. Studying the rash one is currently recruiting and I really appreciate my awesome collaborators in the head and neck and thoracic group which are helping to recruit patients. And that’s to better understand the
microbiome of the populations or option
and see how changes in the microflora
can be associated with the severity of
the rash and response to rash treatment.
And then there’s a company that we’re
working with that’s developing a novel probiotic with staff epidermal
disappointment to look to see if this is going to reduce secondary
infections with staff wareus,
which are commonly associated with severe rashes.
And so this is in development hoping to do this trial next year.
So shifting gears,
other targeted agents, which we see a lot of toxicities from in the breast group. They heard two inhibitors as well as American hitters used for various cancers can actually share some of the properties of the EGFR inhibitor. Reactions will often see folliculitis, eruptions and acne or form rashes. However, they usually less severe and less frequent. I wanted to talk about another very important toxicity which comes to clinic and that’s the hand foot skin reaction.
So these usually develop from the antiangiogenesis agents, some of which we just heard about which are used in the paddle cellular carcinoma such as the anti veg F agents. And here's a list of the FDA approved ones and so this seems to be one of those toxicities which just so frequently impacts patients quality of life. They have a hard time being able to work to do their daily routine. It very often impacts their activities of daily living. Patients usually present early on. We just kind of thickening or hyperkeratosis of the palms and soles,
but then over time they get these very painful.

Callous is, sometimes they are inflamed and then in the severe cases we even see blisters develop as well.

This rash can be associated with very painful dysaesthesia with sometimes will use gabapentinoids like pregabalin or gabapentin to help assist with at this stage as well.

These drugs also are associated with genital eruptions as well as splinter hemorrhages on the nails. So we don’t really have great treatments
00:42:27.264 --> 00:42:29.966 for the hand foot skin reaction right now.
NOTE Confidence: 0.7819162
00:42:29.970 --> 00:42:31.274 Unfortunately, many patients don’t
NOTE Confidence: 0.7819162
00:42:31.274 --> 00:42:33.230 respond to moisturizers and karata lytic,
NOTE Confidence: 0.7819162
00:42:33.230 --> 00:42:34.810 or topical steroid ointments and
NOTE Confidence: 0.7819162
00:42:34.810 --> 00:42:36.820 so dose reduction is often needed.
NOTE Confidence: 0.7819162
00:42:36.820 --> 00:42:39.244 So we’re doing a study looking at a
NOTE Confidence: 0.7819162
00:42:39.244 --> 00:42:40.669 novel topical nitroglycerin ointment
NOTE Confidence: 0.7819162
00:42:40.669 --> 00:42:43.308 to treat grade two or grade three
NOTE Confidence: 0.7819162
00:42:43.308 --> 00:42:45.457 hand foot skin rash and the first
NOTE Confidence: 0.7819162
00:42:45.457 --> 00:42:47.904 phase is going to be comparing it to
NOTE Confidence: 0.7819162
00:42:47.904 --> 00:42:49.860 vehicle and then the second phase.
NOTE Confidence: 0.7819162
00:42:49.860 --> 00:42:51.156 Comparing pyren lower percentages
NOTE Confidence: 0.7819162
00:42:51.156 --> 00:42:53.496 and so if you have any patients
NOTE Confidence: 0.7819162
00:42:53.496 --> 00:42:55.524 who present with hand foot skin.
NOTE Confidence: 0.7819162
00:42:55.530 --> 00:42:57.532 On these approved drugs on the left
NOTE Confidence: 0.7819162
00:42:57.532 --> 00:42:59.995 who have great to her Grade 3 and
really most patients eventually get to grade 2 because it’s almost always interfering with her activities.

Please please I’ll refer them to our study. We definitely need to do better in managing this toxicity.

In interest of time, I’m just gonna I’m just briefly highlight that we could spend all day talking about the different targeted agents in the toxicities I see.

Since you were on or Brewton if for...
CLL often get perperek eruptions, folliculitis patients with breast cancer on PR, 3 kinase inhibitors, and get really terrible. Morbilliform exanthems some requiring the use of Prednisone so wanted to turn now to immune checkpoint inhibitors. Because I think you pennis toxicities are really important. To discuss with this class of cancer cancer therapy. And so all great rash, plus parictis it kind of tally. It all can occur in up to 50% of patients on checkpoint inhibitors at one point in time during their treatment.
This is especially true of patients who are on combination CTL, a foreign PD one therapy and the way that I think about the toxicities from the checkpoint inhibitors is categorized them into those that are the most frequent that we see which are the morbilliform rashes, the lichenoid rash, which I’ll discuss a bit more about the exame and the parictis as well as psoriasis. And then there’s the whole category of autoimmune disorders which occur as immune related adverse events such as diddle I go and bullous pemphigoid.
which I'll discuss more about as well.

Fortunately, the severe rashes, Fortunately, the severe rashes, Fortunately, the severe rashes,

the life threatening Stevens Johnson the life threatening Stevens Johnson the life threatening Stevens Johnson

ones we've seen them, ones we've seen them, ones we've seen them,

but they're not. but they're not. but they're not.

They’re not common, They’re not common, They’re not common,

and then there’s kind of the and then there’s kind of the and then there’s kind of the

miscellaneous category of those that miscellaneous category of those that miscellaneous category of those that

are granulomatis like sarcoid for those are granulomatis like sarcoid for those are granulomatis like sarcoid for those

involving the panniculus or the fassia. involving the panniculus or the fassia. involving the panniculus or the fassia.

So this is actually one of the So this is actually one of the So this is actually one of the

largest studies out there. largest studies out there. largest studies out there.

Looking at the different branches Looking at the different branches Looking at the different branches

from in therapy that we published from in therapy that we published from in therapy that we published

a couple of years ago and it was a a couple of years ago and it was a a couple of years ago and it was a

retrospective retrospective study retrospective retrospective study retrospective retrospective study
of over 100 rashes that we saw in the ankle during clinic and we found is that they really have many different clinical and histopathologic morphologies here and a lot of them resembled idiopathic dermatosis that we treat in dermatology. For patients who are not on checkpoint inhibitors. If you take a look at the yellow box I highlighted kind of the top five and what’s interesting about this is that a lot of these common rashes actually develop many months into therapy. The most common one can be sometimes
six months into treatment, and I think that’s important because patients don’t always realize or put together that their new rashes because of their immune therapy, and in some of the oncologist who are less familiar with these toxicities, also may not. And so I think that’s important to keep in mind that you can definitely get late toxicities to write. This is a very prominent feature.

In most of these containers, toxicities fortunately were able to manage these patients in the vast majority of time,
topically by 20% of patients required Prednisone because of the severity of the rash and 25% had disruption of immune therapy at some point, sometimes before they saw me in clinic, or sometimes because the rash progressed.

But really, the vast majority can remain on immune therapy. It was just the cases of Stevens Johnson, a really bad bullous pemphigoid where immune therapy was discontinued and another important concept here is for the rashes. That do recur after Prednisone or that persist.
Targeting the dermatosis in a more efficient way is probably going to be the future of how these rashes are treated and so we’ve had a great deal of success using things like asset reading for the psoriasis or lichenoid rash Om Alisme after methotrexate for the Bulls tend to glide and the TNF inhibitors for Stevens Johnson, which is how we treat it typically. More recently for the cases that are not associated with checkpoint, I wanted to take a moment to discuss that the lichenoid dermatitis.
is we throw around the term lichenoid and I’m not sure if our colleagues in meddock or familiar with it and so like in what looks like in which an Organism that grows on trees kind of scaly and crusty looks kind of like the rash does. And then there’s the histologic term of lichenoid dermatitis which is an interface dermatitis with the bandlike infiltrate of lymphocytes ANAN. This is the most common histopathologic finding that we see in the skin. And so the lichenoid rash can occur.
in up to a third quarter to 1/3 of patients on PD one and PD Wagon one agents.

And this is kind of a more severe example highlighting the pink violaceous scaly patches and plaques. Here’s a patient who responded to Acitretin were very persistent Palmer planter involvement and he did not do as well with topical steroids or even a short course of Prednisone.

I also wanted to highlight that this lichenoid rash can involve the mucosa, and when that occurs, it can really be quite severe with ulcerations on the genitals as well as the oral mucosa.
Anan this this this clearly is very painful and we were very low threshold for Prednisone in these cases. Sometimes we try things like hydroxychloroquine in those that persist. So in addition to the lichenoid rash from checkpoint inhibitors, we can also see eczematous presentations. So here’s a typical scenario of a patient with psoriasis, then goes on checkpoint.
inhibitor therapy and flares,
and she responded very well to phototherapy,
which is a really nice non
systemic option for these patients.
Here’s an example of widespread eczema,
and here’s a patient that I share with
Doctor Goldberg who just developed just
severe itch and she comes to clinic,
covered in bandages and
explorations and she eventually.
Did somewhat better with pre
gabelein and phototherapy,
so just highlighting that the different
the spectrum of these papulosquamous
rash as we call them from dermatology.
So both paperboy is one of those
rashes which is not common, but it’s a very important one because it has a great deal of associated morbidity with it and so for those who aren’t familiar with it, it’s an autoimmune blistering disease with deposition of IgG and complement at the dermal epidermal junction is seen here in my patients tissue sample and patients also make autoantibodies against BP 180, so we conducted a study a few years ago at our uncle during clinic and we found that about 1% of the patients on checkpoint inhibitors
With PD one or PD wagon one. Based on our pharmacy, this rash so it’s not common, but it definitely can be quite extensive and the latency is usually four to six months. Clinically, patients will often present with just worsening queritis even before the onset of rash. Then they get these urticaria lesions with tense vesicles and bullae, which can become eroded, and you can also get mucosal involvement as well.
rash is unlike a lot of the more common exanthems and lichenoid rash. These typically require Prednisone due to the severity of the presentation with blisters. We've also had cases which have persisted even after immunotherapy has been stopped, and even after a Prednisone taper likely do too. I'm just immune activation and so for those cases things like Rituxan, MAB formalism, Maverick dupilumab which are biologics, I'll discuss later might be very helpful.
And the one question about that comes up a lot is when to worry about a typical macular papular example, My advice with these cases is obviously, you can grade it based on the body surface area, but when the rash is pink and pure Riddick. It's very reassuring when the rash starts to become this more dusky color. And painful. That's when you really have to worry about a progression to a more severe cutaneous reaction, especially if there is any coastal
00:50:33.066 --> 00:50:35.287 involvement or blisters or any systemic signs
00:50:35.287 --> 00:50:37.387 or symptoms really have a low threshold
00:50:37.448 --> 00:50:39.418 for Prednisone and watching carefully,
00:50:39.420 --> 00:50:41.185 we’ve definitely seen these very
00:50:41.185 --> 00:50:42.950 atypical scenarios where an example
00:50:43.002 --> 00:50:44.838 just progressed and slowly over the
00:50:44.838 --> 00:50:46.752 course of several weeks progressed to
00:50:46.752 --> 00:50:48.660 a Stevens Johnson type of scenario.
00:50:48.660 --> 00:50:50.310 And that’s been that’s been
00:50:50.310 --> 00:50:53.280 published with checkpoint inhibitors,
00:50:53.280 --> 00:50:54.270 than classical Stevens.
00:50:54.270 --> 00:50:56.040 Johnson would just takes off.
00:50:56.040 --> 00:50:57.965 At a very rapid tempo nears examples
00:50:57.965 --> 00:50:59.420 of examples that we’ve seen,
as well as Stevens Johnson from

An I think the future direction

for it for treating these cutaneous
toxicities is is looking at a more
efficient way to shut them down.

Basically treating the dermatosis
in the most targeted approach.

There’s definitely a good amount
of data suggesting that the
use of systemic steroids is,
in general, fine, inappropriate,
and it has has not been shown
to impair tumor response when
treating cutaneous toxicities,
but for those cases that
are just recalcitrant,
I think we’re going to find the use of anti aisle 413 drugs like the pillow mab or anti Ige.
He antibodies like oh Melissa Matthews more frequently.
We already have plenty of biologics used in psoriasis and I think there is mounting data in case series of these being used for checkpoint rash as well as TNS for Stevens Johnson.
Here’s an example of a patient I share with Sarah Weiss who had bullous pemphigoid which kept flaring when we slowly taper the Prednisone.
Eventually, with the concomitant administration of Melissa Map were able to get the patient off criticism. And so in the final moments, I just wanted to highlight it’s not the forgotten child, because we see lots of toxicities from the cytotoxic drugs. But these I think you’re probably more familiar with because they’ve been around for a long time, and definitely, alopecia mucositis are kind of your hallmark toxicities. Nail changes are really important
and he’s come up a lot to my clinic, specially young women with breast and gynecological cancers on taxanes or anthracyclines. They get very painful paronychia subungual hemorrhage. They can lose the nail plate they can become. Co infected, and so I think these toxicities are really important and then there’s the toxic rash of chemotherapy which can be hand foot syndrome or malignant intertrigo flow under the umbrella of toxic erythema of chemo and these reactions occur.
through the ecrivain excretion of chemo in the skin of echoing glands. And we just wanted to do a brief shout out to my awesome research fellow who just matched into dermatology at Cornell. Rihanna and she was very interested in looking at the cutaneous toxicities in patients we’ve seen with skin of color which really make up a large proportion of our clinic. And while the diagnosis in general or similar to patients without skin of color, there’s clearly a very prominent finding of hyperpigmentation, which is very bothersome and very,
very prevalent after a rash are examples of that. Patients who get fatal, I go with darker skin. It’s obviously a lot more noticeable, and then there’s definitely a propensity for starring alopecia, but also just keloid scarring. Here’s an example of a patient with a keloid overport site which responded well to injection of triamcinolone, so I think it’s important to look at how these toxicities differ and in various populations. And in closing went to refer.
patients to our clinic.

I think the short answer is anytime you need a hand, we’re really happy to see these patients. It is a privilege definitely for rashes that are higher grade that are impacting quality of life or that are recalcitrant to kind of conservative management. And definitely anytime there’s a red flag that I mentioned like skin pain, duskiness, blisters or plus definitely send those patients our way.

So in conclusion, I hope you’ll see from this talk that cutaneous toxicities are not just common, but they’re also really important in the

97
overall management of cancer patients.

I hope that Dermot Earley dermatologic intervention can make a difference.

Remember that the EGFR acne reform rash often starts.

It is a sterile rash, but it can often be secondarily infected and you can get these unusual late perperek eruptions as well.

Hand foot skin from the anti angiogenesis drugs and definitely have associated pain.

We don’t have great treatments yet, so please consider referring patients to the study using a novel nitroglycerin.
ointment to treat it and then turning to the checkpoint inhibitor rash. I think the lichenoid one is the important one to know about. It’s common it can have associated parictis and mucosal involvement as well as bullous pemphigoid, which frequently requires systemic therapy. And if there’s any red flag, obviously you know you have to treat these patients aggressively. So I just wanted to thank really all of my colleagues Ann and Metang, Sir John Cradoc, everyone at Smilow who’s supported
our clinic over the years.

I have a really great team from the admins to the nurses to my chief residents, many of which have chosen Uncle Dharmas. Akarere Anatomy very proud and as well my research fellows, an NYCC I. So if you ever have any patients, I'm very always available. You can text me call me. Contact us and we'll gladly see them. So thank you and I'll take any questions.

It's terrific, thank you, Jonathan.

Do you have questions from the audience?

My recollection is that with the B RAF inhibitors there was a serious
problem with squamous cell carcinoma’s is
that yeah so actually had a.
I had a picture of that slide.
I didn’t go into it too much but we had.
We saw a lot of toxicities over the years with the beer at inhibitors,
but with the concomitant administration we’ve actually seen that basically drop down to near near 0 and so you can still get phototoxic rash is another odd things, like everything and awesome,
we’ve not seen squamous cells develop in patients on be right contributors to the American hitter.
Coadministration perfect thank you.

Any other questions?

If not, thank you Jonathan.

Very interesting. Looks like you’re making a lot of progress in managing these disorders.

Thanks for having me.